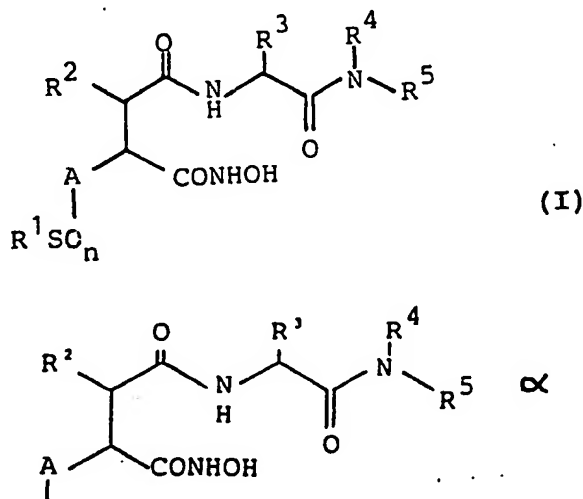




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁵ : C07C 323/62, 323/60, C07D 333/34 C07C 327/32, 317/50, 313/48 A61K 31/13, 31/38</p>	A1	<p>(11) International Publication Number: WO 90/05719</p> <p>(43) International Publication Date: 31 May 1990 (31.05.90)</p>
<p>(21) International Application Number: PCT/GB89/01399</p> <p>(22) International Filing Date: 23 November 1989 (23.11.89)</p> <p>(30) Priority data: 8827305.7 23 November 1988 (23.11.88) GB</p> <p>(71) Applicant (for all designated States except US): BRITISH BIO-TECHNOLOGY LIMITED [GB/GB]; Watlington Road, Cowley, Oxford OX4 5LY (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only) : CAMPION, Colin [GB/GB]; 3 Howe Close, Wheatley, Oxon OX4 5LY (GB). DAVIDSON, Alan, Hornsby [GB/GB]; 27 Newland Mill, Witney, Oxon OX8 6HH (GB). DICKENS, Jonathan, Philip [GB/GB]; Burton House, Park Farm Road, High Wycombe, Bucks HP12 4AF (GB). CRIMMIN, Michael, John [GB/GB]; Oaklea, 64 Fernbank Road, Ascot SL5 8HE (GB).</p>		<p>(74) Agents: SHEARD, Andrew, Gregory et al.; Kilburn & Strode, 30 John Street, London WC1N 2DD (GB).</p> <p>(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, ES (European patent), FI, FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), US.</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>

(54) Title: HYDROXAMIC ACID BASED COLLAGENASE INHIBITORS



(57) Abstract

Compounds of general formula (I), wherein R¹ represents hydrogen or an alkyl, phenyl, thiophenyl, substituted phenyl, phenylalkyl, heterocyclyl, alkylcarbonyl phenacyl or substituted phenacyl group; or, when n = 0, R¹ represents SR^x, wherein R^x represents a group (α); R² represents a hydrogen atom or an alkyl, alkenyl, phenylalkyl, cycloalkylalkyl or cycloalkenylalkyl group; R³ represents an amino acid residue with R or S stereochemistry or an alkyl, benzyl, (C₁-C₆ alkoxy) benzyl or benzyloxy (C₁-C₆ alkyl) group; R⁴ represents a hydrogen atom or an alkyl group; R⁵ represents a hydrogen atom or a methyl group; n is an integer having the value 0, 1 or 2; and A represents a hydrocarbon chain optionally substituted with one or more alkyl, phenyl or substituted phenyl groups; and their salts and N-oxides are collagenase inhibitors and are useful in the management of disease involving tissue degradation and/or the promotion of wound healing. Diseases involving tissue degradation include arthropathy (particularly rheumatoid arthritis), inflammation, dermatological diseases, bone resorption diseases and tumour invasion.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MR	Mauritania
BE	Belgium	GA	Gabon	MW	Malawi
BF	Burkina Faso	GB	United Kingdom	NL	Netherlands
BG	Bulgaria	HU	Hungary	NO	Norway
BJ	Benin	IT	Italy	RO	Romania
BR	Brazil	JP	Japan	SD	Sudan
CA	Canada	KP	Democratic People's Republic of Korea	SE	Sweden
CF	Central African Republic	KR	Republic of Korea	SN	Senegal
CG	Congo	LI	Liechtenstein	SU	Soviet Union
CH	Switzerland	LK	Sri Lanka	TD	Chad
CM	Cameroon	LU	Luxembourg	TG	Togo
DE	Germany, Federal Republic of	MC	Monaco	US	United States of America
DK	Denmark				

1 HYDROXAMIC ACID BASED COLLAGENASE INHIBITORS.

2

3 This invention relates to pharmaceutically and
4 veterinarily active compounds, which are derivatives of
5 hydroxamic acid.

6

7 The compounds of the present invention act as
8 inhibitors of metalloproteases involved in tissue
9 degradation, such as collagenase, which initiates
10 collagen breakdown, stromelysin (proteoglycanase),
11 gelatinase and collagenase (IV). There is evidence
12 implicating collagenase as one of the key enzymes in
13 the breakdown of articular cartilage and bone in
14 rheumatoid arthritis (Arthritis and Rheumatism, 20,
15 1231 - 1239, 1977). Potent inhibitors of collagenase
16 and other metalloproteases involved in tissue
17 degradation are useful in the treatment of rheumatoid
18 arthritis and related diseases in which collagenolytic
19 activity is important. Inhibitors of metalloproteases
20 of this type can therefore be used in treating or
21 preventing conditions which involve tissue breakdown;
22 they are therefore useful in the treatment of
23 arthropathy, dermatological conditions, bone
24 resorption, inflammatory diseases and tumour invasion
25 and in the promotion of wound healing. Specifically,
26 compounds of the present invention may be useful in the
27 treatment of osteopenias such as osteoporosis,
28 rheumatoid arthritis, osteoarthritis, periodontitis,
29 gingivitis, corneal ulceration and tumour invasion.

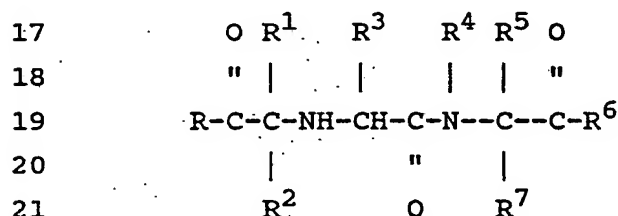
30

31 A number of small peptide like compounds which
32 inhibit metalloproteases have been described. Perhaps
33 the most notable of these are those relating to the

1 angiotensin converting enzyme (ACE) where such
 2 agents act to block the conversion of the decapeptide
 3 angiotensin I to angiotensin II a potent pressor
 4 substance. Compounds of this type are described in
 5 EP-A-0012401.

6
 7 Certain hydroxamic acids have been suggested as
 8 collagenase inhibitors as in US-A-4599361 and
 9 EP-A-0236872. Other hydroxamic acids have been prepared
 10 as ACE inhibitors, for example in US-A-4105789, while
 11 still others have been described as enkephalinase
 12 inhibitors as in US-A-4496540.

13
 14 EP-A-0012401 discloses antihypertensive compounds of
 15 the formula:



22
 23 wherein

24
 25 R and R⁶ are the same or different and are hydroxy,
 26 alkoxy, alkenoxy, dialkylamino alkoxy, acylamino
 27 alkoxy, acyloxy alkoxy, aryloxy, alkyloxy, substituted
 28 aryloxy or substituted aralkoxy wherein the substituent
 29 is methyl, halo, or methoxy, amino, alkylamino,
 30 dialkylamino, aralkylamino or hydroxyamino;

31
 32
 33

1 R^1 is hydrogen, alkyl of from 1 to 20 carbon atoms,
2 including branched, cyclic and unsaturated alkyl
3 groups;

4
5 substituted alkyl wherein the substituent is halo,
6 hydroxy, alkoxy, aryloxy amino, alkylamino,
7 dialkylamino, acrylamino, arylamino, guanidino,
8 imidazolyl, indolyl, mercapto, alkylthio, arylthio,
9 carboxy, carboxamido, carbalkoxy, phenyl, substituted
10 phenyl wherein the substituent is alkyl, alkoxy or
11 halo; aralkyl or heteroaralkyl, aralkenyl or
12 heteroaralkenyl, substituted aralkyl, substituted
13 heteroaralkyl, substituted aralkenyl or substituted
14 heteroaralkenyl, wherein the substituent is halor or
15 dihalo, alkyl, hydroxy, alkoxy, amino, aminomethyl,
16 acrylamino, dialkylamino, alkylamino, carboxyl,
17 haloalkyl, cyano or sulphonamido, aralkyl or
18 heteroaralkyl substituted on the alkyl portion by
19 amino or acylamino;

20
21 R^2 and R^7 are hydrogen or alkyl;

22
23 R^3 is hydrogen, alkyl, phenylalkyl,
24 aminomethylphenylalkyl, hydroxyphenylalkyl,
25 hydroxyalkyl, acetylaminoalkyl, acylaminoalkyl,
26 acylaminoalkyl aminoalkyl, dimethylaminoalkyl,
27 haloalkyl, guanidinoalkyl, imidazolylalkyl,
28 indolylalkyl, mercaptoalkyl and alkylthioalkyl;

29
30 R^4 is hydrogen or alkyl;

31

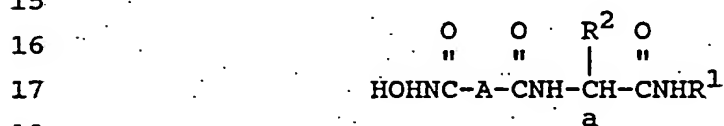
32

33

1 R^5 is hydrogen, alkyl, phenyl, phenylalkyl,
 2 hydroxyphenylalkyl, hydroxyalkyl, aminoalkyl,
 3 guanidinoalkyl, imidazolylalkyl, indolylalkyl,
 4 mercaptoalkyl or alkylthioalkyl;

5
 6 R^4 and R^5 may be connected together to form an alkylene
 7 bridge of from 2 to 4 carbon atoms, an alkylene bridge
 8 of from 2 to 3 carbon atoms and one sulphur atom, an
 9 alkylene bridge of from 3 to 4 carbon atoms containing
 10 a double bond or an alkylene bridge as above,
 11 substituted with hydroxy, alkoxy or alkyl and the
 12 pharmaceutically acceptable salts thereof.

13
 14 US-A-4599361 discloses compounds of the formula:



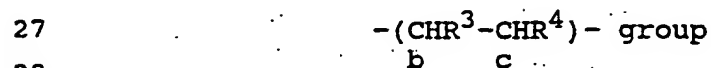
15
 16
 17
 18
 19 wherein

20 R^1 is C_1 - C_6 alkyl;

21 R^2 is C_1 - C_6 alkyl, benzyl, benzyloxybenzyl, (C_1 - C_6
 22 alkoxy)benzyl or benzyloxy(C_1 - C_6 alkyl);

23 a is a chiral centre with optional R or S
 24 stereochemistry;

25 A is a



28
 29 or a $-(\text{CR}^3=\text{CR}^4)-$ group wherein b and c are chiral
 30 centres with optional R or S stereochemistry;

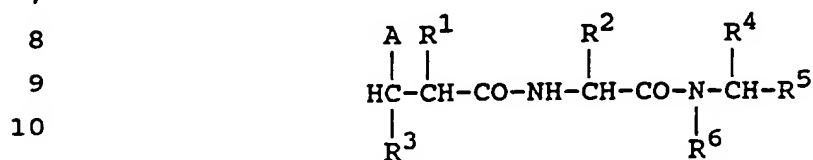
31

32

33

1 R^3 is hydrogen, C_1-C_6 alkyl, phenyl or phenyl(C_1-C_6
 2 alkyl) and R^4 is hydrogen, C_1-C_6 alkyl, phenyl(C_1-C_6
 3 alkyl), cycloalkyl or cycloalkyl(C_1-C_6 alkyl).

4
 5 EP-A-0236872 discloses generically compounds of the
 6 formula



11
 12
 13 wherein

14
 15 A represents a group of the formula $HN(OH)-CO-$ or
 16 $HCO-N(OH)-$;

17
 18 R^1 represents a C_2-C_5 alkyl group;

19
 20 R^2 represents the characterising group of a natural
 21 alpha-amino acid in which the functional group can be
 22 protected, amino groups may be acylated and carboxyl
 23 groups can be amidated, with the proviso that R^2 can
 24 not represent hydrogen or a methyl group;

25
 26 R^3 represents hydrogen or an amino, hydroxy, mercapto,
 27 C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 acylamino,
 28 C_1-C_6 -alkylthio, aryl-(C_1-C_6 alkyl)-,
 29 amino-(C_1-C_6 -alkyl)-, hydroxy(C_1-C_6 -alkyl)-,
 30 mercapto(C_1-C_6 alkyl) or carboxy(C_1-C_6 alkyl) group,

31

32

33

1 wherein the amino, hydroxy, mercapto or carboxyl groups
2 can be protected and the amino groups may be acylated
3 or the carboxyl groups may be amidated;

4
5 R^4 represents hydrogen or a methyl group;

6
7 R^5 represents hydrogen or a C_1-C_6 acyl, C_1-C_6 alkoxy-
8 C_1-C_6 alkyl, di(C_1-C_6 -alkoxy)methylene, carboxy, (C_1-C_6
9 alkyl)carbiny, (C_1-C_6 alkoxy)carbiny, arylmethoxy
10 carbiny, (C_1-C_6 alkyl)amino carbiny or arylamino
11 carbiny group; and

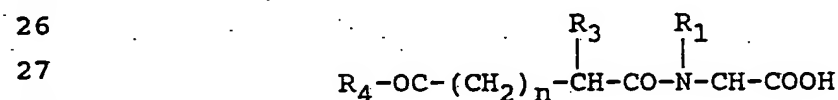
12
13 R^6 represents hydroxy or a methylene group; or

14
15 R^2 and R^4 together represent a group- $(CH_2)_n$ -, wherein n
16 represents a number from 4 to 11; or

17
18 R^4 and R^5 together represent a trimethylene group;

19
20 and pharmaceutically acceptable salts of such
21 compounds, which are acid or basic.

22
23 US-A-4105789 generically discloses compounds which have
24 the general formula



28
29 and salts thereof, wherein

30
31 R_1 is hydrogen, lower alkyl, phenyl lower alkylene,
32 hydroxy-lower alkylene, hydroxyphenyl lower
33 alkylene, amino-lower alkylene, guanidine lower

1 alkylene, mercapto-lower alkylene, lower
2 alkyl-mercapto-lower alkylene, imidazolyl lower
3 alkylene, indolyl-lower alkylene or carbamoyl
4 lower alkylene;

5 R₂ is hydrogen or lower alkyl;

6 R₃ is lower alkyl or phenyl lower alkylene;

7 R₄ is hydroxy, lower alkoxy or hydroxyamino; and

8 n is 1 or 2.

9

10 US-A-4496540 discloses compounds of the general
11 formula:

12

13 A-B-NHOH

14

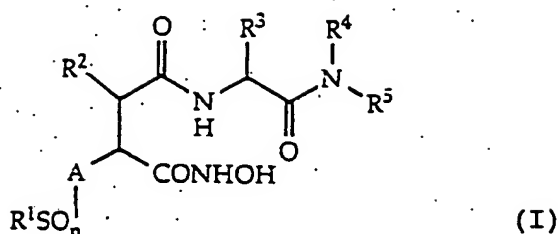
15 wherein A is one of the aromatic group-containing amino
16 acid residues L-tryptophyl, D-tryptophyl, L-tyrosyl,
17 D-tyrosyl, L-phenylalanyl, or D-phenylalanyl, and B is
18 one of the amino acids glycine, L-alanine, D-alanine,
19 L-leucine, D-leucine, L-isoleucine, or D-isoleucine;
20 and pharmaceutically acceptable salts thereof.

21

22 It would however be desirable to improve on the
23 solubility of known collagenase inhibitors and/or
24 stomelysin inhibitors (whether as the free base or the
25 salt) and, furthermore, increases in activity have also
26 been sought. It is not a simple matter, however, to
27 predict what variations in known compounds would be
28 desirable to increase or even retain activity; certain
29 modifications of known hydroxamic acid derivatives have
30 been found to lead to loss of activity.

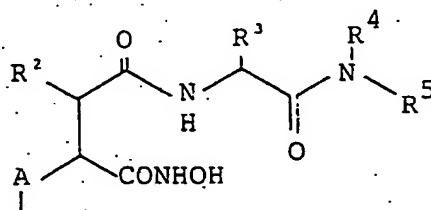
31

32 According to a first aspect of the invention, there is
33 provided a compound of general formula I:



wherein:

R^1 represents a $\text{C}_1\text{-C}_6$ alkyl, phenyl, thiophenyl, substituted phenyl, phenyl($\text{C}_1\text{-C}_6$)alkyl, heterocyclyl, ($\text{C}_1\text{-C}_6$)alkylcarbonyl, phenacyl or substituted phenacyl group; or, when $n = 0$, R^1 represents SR^x , wherein R^x represents a group:



R^2 represents a hydrogen atom or a $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkenyl, phenyl($\text{C}_1\text{-C}_6$)alkyl, cycloalkyl($\text{C}_1\text{-C}_6$)alkyl or cycloalkenyl($\text{C}_1\text{-C}_6$)alkyl group;

R^3 represents an amino acid side chain or a $\text{C}_1\text{-C}_6$ alkyl, benzyl, ($\text{C}_1\text{-C}_6$ alkoxy)benzyl, benzyloxy($\text{C}_1\text{-C}_6$ alkyl) or benzyloxybenzyl group;

R^4 represents a hydrogen atom or a $\text{C}_1\text{-C}_6$ alkyl group;

R^5 represents a hydrogen atom or a methyl group;

1 n is an integer having the value 0, 1 or 2; and

2

3 A represents a C₁-C₆ hydrocarbon chain, optionally
4 substituted with one or more C₁-C₆ alkyl, phenyl
5 or substituted phenyl groups;

6

7 or a salt thereof.

8

9 Hereafter in this specification, the term "compound"
10 includes "salt" unless the context requires otherwise.

11

12 As used herein the term "C₁-C₆ alkyl" refers to a
13 straight or branched chain alkyl moiety having from
14 one to six carbon atoms, including for example,
15 methyl, ethyl, propyl, isopropyl, butyl, t-butyl,
16 pentyl and hexyl, and cognate terms. (such as "C¹-C⁶
17 alkoxy") are to be construed accordingly.

18

19 The term "C₁-C₆ alkenyl" refers to a straight or
20 branched chain alkyl moiety having one to six carbons
21 and having in addition one double bond, of either E or
22 Z stereochemistry where applicable. This term would
23 include, for example, an alpha, beta-unsaturated
24 methylene group, vinyl, 1-propenyl, 1- and 2-butenyl
25 and 2-methyl-2-propenyl.

26

27 The term "cycloalkyl" refers to a saturated
28 alicyclic moiety having from 3 to 8 carbon atoms
29 and includes for example, cyclopropyl, cyclobutyl,
30 cyclopentyl and cyclohexyl.

31

32

33

1 The term "cycloalkenyl" refers to an unsaturated
2 alicycle having from 3 to 8 carbon atoms and includes
3 cyclopropenyl, cyclobutenyl and cyclopentenyl,
4 cyclohexenyl.

5
6 The term "substituted", as applied to a phenyl or other
7 aromatic ring, means substituted with up to four
8 substituents each of which independently may be C₁-C₆
9 alkyl, C₁-C₆ alkoxy, hydroxy, thiol, C₁-C₆ alkylthiol,
10 amino, halo (including fluoro, chloro, bromo and iodo),
11 trifluoromethyl or nitro.

12
13 The term "amino acid side chain" means a characteristic
14 side chain attached to the -CH(NH₂)(COOH) moiety in the
15 following R or S amino acids: glycine, alanine, valine,
16 leucine, isoleucine, phenylalanine, tyrosine,
17 tryptophan, serine, threonine, cysteine, methionine,
18 asparagine, glutamine, lysine, histidine, arginine,
19 glutamic acid and aspartic acid.

20
21 The term "hydrocarbon chain" includes alkylene,
22 alkenylene and alkynylene chains of from 1 to 6 carbon
23 atoms. Preferably the carbon atom of the hydrocarbon
24 chain nearest to the hydroxamic acid group is a
25 methylene carbon atom.

26
27 There are several chiral centres in the compounds
28 according to the invention because of the presence of
29 asymmetric carbon atoms. The presence of several
30 asymmetric carbon atoms gives rise to a number of
31 diastereomers with the appropriate R or S
32 stereochemistry at each chiral centre. General formula
33 I and, where appropriate, all other formulae in this

1 specification are to be understood to include all such
2 stereoisomers and mixtures (for example racemic
3 mixtures) thereof. Compounds in which the chiral centre
4 adjacent the substituent R^3 has S stereochemistry
5 and/or the chiral centre adjacent the substituent R^2
6 has R stereochemistry are preferred.

7

8 Further or other preferred compounds include those in
9 which, independently or in any combination:

10

11 R^1 represents a hydrogen atom or a C_1 - C_4 alkyl,
12 phenyl, thiophenyl, benzyl, acetyl or benzoyl
13 group;

14

15 R^2 represents a C_3 - C_6 alkyl (for example isobutyl)
16 group;

17

18 R^3 represents a benzyl or 4-(C_1 - C_6)alkoxyphenylmethyl
19 or benzyloxybenzyl group;

20

21 R^4 represents a C_1 - C_4 alkyl (for example methyl)
22 group; and

23

24 R^5 represents a hydrogen atom.

25

26 Particularly preferred compounds include:

27

28 1. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthio-
29 methyl)-succinyl]-L-phenylalanine-N-methylamide,

30

31 2. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenyl-
32 thio-methyl)succinyl]-L-phenylalanine-
33 N-methylamide,

- 1 3. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(benzylthio-
2 methyl) succinyl]-L-phenylalanine-N-methylamide,
3
- 4 4. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(acetylthio-
5 methyl)succinyl]-L-phenylalanine-N-methylamide and
6
- 7 5. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiolmethyl)
8 succinyl]-L-phenylalanine-N-methylamide
9
- 10 6. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(benzoylthio-
11 methyl)succinyl]-L-phenylalanine-N-methylamide
12
- 13 7. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(pivaloyl-
14 thiomethyl)succinyl]-L-phenylalanine-N-methyl-
15 amide
16
- 17 8. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenyl-
18 thiomethyl)succinyl]-L-phenylalanine-N-methyl-
19 amide sodium salt
20
- 21 9. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxy-
22 phenyl-thiomethyl)succinyl]-L-phenylalanine-N-
23 methylamide
24
- 25 10. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxy-
26 phenylthiomethyl)succinyl]-L-phenylalanine-N-
27 methylamide
28
- 29 11 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thio-
30 phenethiomethyl)succinyl]-L-phenylalanine-N-
31 methylamide sodium salt
32
33

- 1 12. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxy-
2 phenylthiomethyl)succinyl]-L-phenylalanine-N-
3 methylamide sodium salt
4
- 5 13. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-tert-
6 butylphenylthiomethyl)succinyl]-L-phenylalanine-
7 N-methylamide
8
- 9 14. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2,4-di-
10 methylphenylthiomethyl)succinyl]-L-phenyl-
11 alanine-N-methylamide
12
- 13 15. bis-S, S' - { [4 (N-Hydroxyamino-2R-isobutyl-
14 3S-(thiomethyl)succinyl]-L-phenylalanine-N-methyl-
15 amide) disulphide
16
- 17 16. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-bromo-
18 phenylthio-methyl)succinyl]-L-phenylalanine-N-
19 methylamide
20
- 21 17. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-chloro-
22 phenylthiomethyl)succinyl]-L-phenylalanine-N-
23 methylamide
24
- 25 18. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-methyl-
26 phenylthiomethyl)succinyl]-L-phenylalanine-N-
27 methylamide
28
- 29 19. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-acetyl)-
30 aminophenylthiomethyl)succinyl]-L-phenylalanine-
31 N-methylamide
32
33

- 1 20. [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenyl-
2 sulphinylmethylsuccinyl]-L-phenylalanine-N-methyl-
3 amide
4
- 5 21. [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenyl-
6 sulphonylmethylsuccinyl]-L-phenylalanine-N-methyl-
7 amide
8
- 9 22. [4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenyl-
10 sulphinylmethyl-succinyl]-L-phenylalanine-N-
11 methylamide
12
- 13 23. [4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenyl-
14 sulphonylmethyl-succinyl]-L-phenylalanine-N-
15 methylamide
16
- 17 24. [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenyl-
18 sulphonylmethyl-succinyl]-L-phenylalanine-N-
19 methylamide sodium salt
20
- 21 25. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(isobutyl-
22 oxycarbonylamino)phenyl)thiomethyl-succinyl]-L-
23 phenylalanine-N-methylamide
24
- 25 26. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-methyl-N-
26 (tert-butoxycarbonyl)-glycylamino)phenyl)thio-
27 methylsuccinyl]-L-phenylalanine-N-methylamide
28

29 and, where appropriate, their salts. Compounds 2 and 5
30 are especially preferred and compound 2 is the most
31 preferred, because of its good collagenase-inhibiting
32 and protoglycanase-inhibiting activities.
33

1 Compounds of general formula I may be prepared by any
 2 suitable method known in the art and/or by the
 3 following process, which itself forms part of the
 4 invention.

5

6 According to a second aspect of the invention, there is
 7 provided a process for preparing a compound of general
 8 formula I as defined above, the process comprising:

9

10 (a) deprotecting a compound of general formula II

11

12

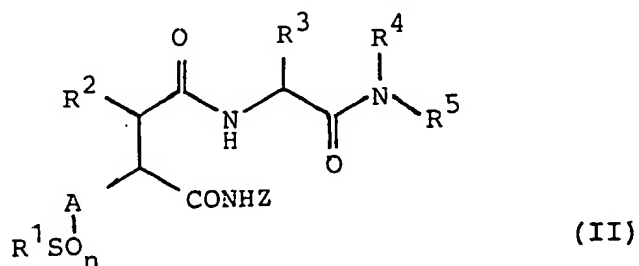
13

14

15

16

17



18

wherein:

19

20 R^1 , R^2 , R^3 , R^4 , R^5 , A and n are as defined in
 21 general formula I and Z represents a protective
 22 group such as a benzyl group; or

23

24 (b) reacting a compound of general formula III

25

26

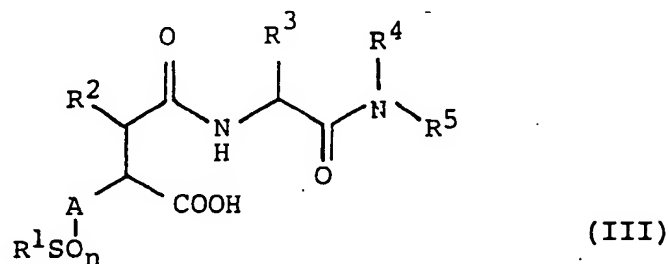
27

28

29

30

31



32

wherein:

33

1 R^1 , R^2 , R^3 , R^4 , R^5 , A and n are as defined in
 2 general formula I,

3

4 with hydroxylamine or a salt thereof; or

5

6 (c) reacting a compound of general formula VIA

7

8

9

10

11

12

13

14 wherein

15

16 R^2 , R^3 , R^4 and R^5 are as defined in general
 17 formula I,

18

19 either with a thiol of the general formula R^1S , wherein
 20 R^1 is as defined in general formula I to give a
 21 compound of general formula I in which A represents a
 22 methylene group and n is 0,

23

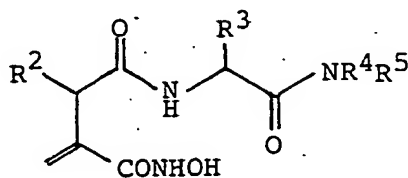
24 or with a cuprate of the general formula $(R^1S-A^1)_2CuLi$,
 25 wherein R^1 is as defined in general formula I and A^1 is
 26 such that $-A^1-CH_2-$ is identical to $-A-$, as defined in
 27 general formula I.

28

29 (d) optionally after step (a), step (b) or step (c)
 30 converting a compound of general formula I into another
 31 compound of general formula I.

32

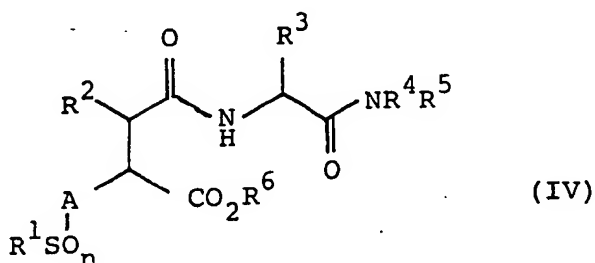
33



(VIA)

1 Compounds of general formula I which are sulfoxides or
 2 sulphones can be derived from thiol compounds of
 3 general formula I by oxidation. Alternatively, thiols
 4 of general formula II or III may be oxidised.
 5 Compounds of general formula I which are disulphides
 6 (ie compounds wherein R^1 represents SR^X) may be derived
 7 from thiol esters of general formula I by milk
 8 oxidation, for example in air.

9
 10 A compound of general formula II may be prepared from a
 11 compound of general formula III by reaction with an
 12 O-protected (such as benzyl) hydroxylamine. A compound
 13 of general formula III may be prepared by
 14 deesterification (such as hydrolysis) of an ester of the
 15 general formula IV



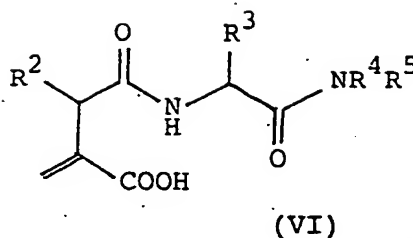
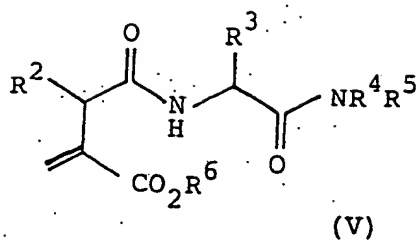
22 wherein:

23
 24 R^1 , R^2 , R^3 , R^4 , R^5 , A and n are as defined in
 25 general formula I and R^6 represents C_1 - C_6 alkyl,
 26 phenyl C_1 - C_6 alkyl or substituted phenyl C_1 - C_6
 27 alkyl.

28
 29 A compound of general formula IV can be prepared from
 30 an ester of general formula V or an acid of general
 31 formula VI

32

33



wherein:

R^2 , R^3 , R^4 and R^5 are as defined in general formula I and R^6 represents $\text{C}_1\text{-C}_6$ alkyl, phenyl $\text{C}_1\text{-C}_6$ alkyl or substituted phenyl $\text{C}_1\text{-C}_6$ alkyl

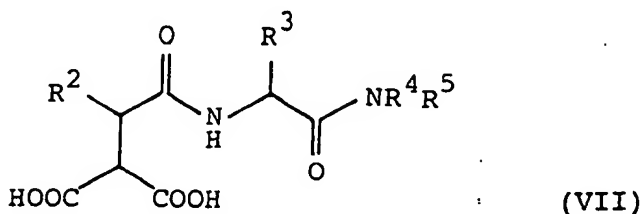
by reaction with a thiol R^1SH , wherein R^1 is as defined in general formula I, to give compounds wherein A represents a methylene group,

or by reaction with a cuprate of the general formula $(\text{R}^1\text{S-A}^1)_2\text{CuLi}$, wherein R^1 is as defined in general formula I and A^1 is such that $-\text{A}^1\text{-CH}_2-$ is identical to $-\text{A}-$, as defined in general formula I.

Esters of general formula V can be prepared by esterifying acids of general formula VI with an appropriate alcohol R^6OH or other esterifying agent.

Compounds of general formula VIA can be prepared by reacting compounds of general formula VI with hydroxylamine or a salt thereof.

1 An acid of general formula VI can be prepared by
 2 reacting a malonic acid derivative of general formula
 3 VII

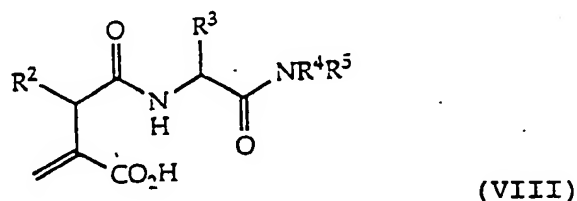


9
 10 wherein:

11
 12 R^2 , R^3 , R^4 and R^5 are as defined in general
 13 formula I

14
 15 with formaldehyde in the presence of pyridine.

16
 17 An acid of general formula VII can in turn be prepared
 18 by desterifying (for example hydrolysing) a compound of
 19 general formula VIII



26
 27 wherein:

28
 29 R^2 , R^3 , R^4 and R^5 are as defined in general
 30 formula I and R^6 represents $\text{C}_1\text{-C}_6$ alkyl, phenyl
 31 $\text{C}_1\text{-C}_6$ alkyl or substituted phenyl $\text{C}_1\text{-C}_6$ alkyl.

32
 33

1 A compound of general formula VIII can be prepared by
 2 reacting a compound of general formula IX with a
 3 compound of general formula X

4

5

6

7

8

9

10

11 wherein:

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

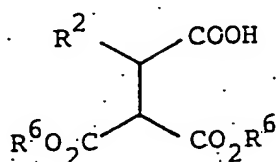
29

30

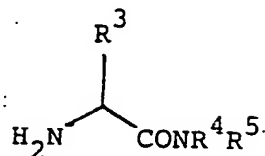
31

32

33



(IX)

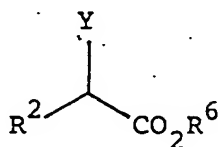


(X)

13 R^2 , R^3 , R^4 and R^5 are as defined in general
 14 formula I and R^6 represents $\text{C}_1\text{-C}_6$ alkyl, phenyl
 15 $\text{C}_1\text{-C}_6$ alkyl or substituted phenyl $\text{C}_1\text{-C}_6$ alkyl.

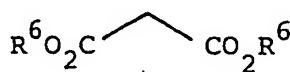
17 The starting materials and other reagents are either
 18 available commercially or can be synthesised by simple
 19 chemical procedures.

21 For example, a substituted acid of general formula IX
 22 may be prepared by reacting an ester of the general
 23 formula XI



(XI)

29 wherein Y represents halo and R^5 is as defined above
 30 and R^2 and R^6 as defined above, with a malonate
 31 derivative of the general formula XII



(XII)

1 wherein R⁶ is as defined above with the proviso that
2 when R⁶ is aromatic in general formula XI it is
3 aliphatic in general formula XII or vice versa, and
4 selectively de-esterifying.

5
6 Compounds of general formula XI can simply be derived
7 from amino acids, which can be obtained in
8 enantiomerically pure form, enabling a choice of
9 optically active compounds of general formula I to be
10 prepared.

11
12 Compounds of general formulae II and III are valuable
13 intermediates in the preparation of compounds of
14 general formula I. According to a third aspect of the
15 invention, there is therefore provided a compound of
16 general formula II. According to a fourth aspect of the
17 invention, there is provided a compound of general
18 formula III.

19
20 As mentioned above, compounds of general formula I are
21 useful in human or veterinary medicine as they are
22 active inhibitors, of metalloproteases involved in
23 tissue degradation.

24
25 According to a fifth aspect of the invention, there is
26 provided a compound of general formula I for use in
27 human or veterinary medicine, particularly in the
28 management (by which is meant treatment of prophylaxis)
29 of disease involving tissue degradation, in particular
30 rheumatoid arthritis, and/or in the promotion of wound
31 healing.

32
33

1 According to a sixth aspect of the invention, there is
2 provided the use of a compound of general formula I in
3 the preparation of an agent for the management of
4 disease involving tissue degradation, particularly
5 rheumatoid arthritis, and/or in the promotion of wound
6 healing. Compounds of general formula I can therefore
7 be used in a method of treating disease involving
8 tissue degradation, particularly rheumatoid arthritis,
9 and/or in a method of promoting wound healing, the
10 method in either case comprising administering to a
11 human or animal patient an effective amount of a
12 compound of general formula I.

13

14 The potency of compounds of general formula I to act
15 as inhibitors of collagenase (a metalloprotease
16 involved in tissue degradation) was determined by the
17 procedure of Cawston and Barrett, (Anal. Biochem., 99,
18 340-345, 1979) and their potency to act as inhibitors
19 of stromelysin was determined using the procedure of
20 Cawston et al (Biochem. J., 195, 159-165 1981), both of
21 which techniques are to be described more fully in the
22 examples and are incorporated by reference herein so
23 far as the law allows.

24

25 According to a seventh aspect of the invention, there
26 is provided a pharmaceutical or veterinary formulation
27 comprising a compound of general formula I and a
28 pharmaceutically and/or veterinarily acceptable
29 carrier. One or more compounds of general formula I may
30 be present in association with one or more non-toxic
31 pharmaceutically and/or veterinarily acceptable
32 carriers and/or diluents and/or adjuvants and if
33 desired other active ingredients.

1 According to an eighth aspect of the invention, there
2 is provided a process for the preparation of a
3 pharmaceutical or veterinary formulation in accordance
4 with the seventh aspect, the process comprising
5 admixing a compound of general formula I and a
6 pharmaceutically and/or veterinarily acceptable
7 carrier.

8
9 Compounds of general formula I may be formulated for
10 administration by any route and would depend on the
11 disease being treated. The compositions may be in
12 the form of tablets, capsules, powders, granules,
13 lozenges, liquid or gel preparations, such as oral,
14 topical, or sterile parental solutions or
15 suspensions.

16
17 Tablets and capsules for oral administration may be in
18 unit dose presentation form, and may contain
19 conventional excipients such as binding agents, for
20 example syrup, acacia, gelatin, sorbitol, tragacanth,
21 or polyvinyl-pyrrolidone; fillers for example lactose,
22 sugar, maize-starch, calcium phosphate, sorbitol or
23 glycine; tableting lubricant, for example
24 magnesium stearate, talc, polyethylene glycol or
25 silica; disintegrants, for example potato starch, or
26 acceptable wetting agents such as sodium lauryl
27 sulphate. The tablets may be coated according to
28 methods well known in normal pharmaceutical practice.
29 Oral liquid preparations may be in the form of, for
30 example, aqueous or oily suspensions, solutions,
31 emulsions, syrups or elixirs, or may be presented as a
32 dry product for reconstitution with water or other
33 suitable vehicle before use. Such liquid

1 preparations may contain conventional additives such
2 as suspending agents, for example sorbitol, syrup,
3 methyl cellulose, glucose syrup, gelatin,
4 hydrogenated edible fats; emulsifying agents, for
5 example lecithin, sorbitan monooleate, or acacia;
6 non-aqueous vehicles (which may include edible
7 oils), for example almond oil, fractionated coconut
8 oil, oily esters such as glycerine, propylene glycol,
9 or ethyl alcohol; preservatives, for example methyl or
10 propyl p-hydroxybenzoate or sorbic acid, and if
11 desired conventional flavouring or colouring agents.

12
13 The dosage unit involved in oral administration may
14 contain from about 1 to 250 mg, preferably from about
15 25 to 250 mg of a compound of general formula I. A
16 suitable daily dose for a mammal may vary widely
17 depending on the condition of the patient. However,
18 a dose of a compound of general formula I of about 0.1
19 to 300mg/kg body weight, particularly from about 1 to
20 100 mg/kg body weight may be appropriate.

21
22 For topical application to the skin the drug may be
23 made up into a cream, lotion or ointment. Cream or
24 ointment formulations that may be used for the drug
25 are conventional formulations well known in the art,
26 for example, as described in standard text books of
27 pharmaceuticals such as the British Pharmacopoeia.

28
29 For topical applications to the eye, the drug may be
30 made up into a solution or suspension in a suitable
31 sterile aqueous or non-aqueous vehicle. Additives,
32 for instance buffers such as sodium metabisulphite or
33 disodium edeate; preservatives including bactericidal

1 and fungicidal agents, such as phenyl mercuric
2 acetate or nitrate, benzalkonium chloride or
3 chlorohexidine, and thickening agents such as
4 hypromellose may also be included.

5
6 The dosage employed for the topical administration
7 will, of course, depend on the size of the area being
8 treated. For the eyes each dose will be typically in
9 the range from 10 to 100 mg of the compound of general
10 formula I.

11
12 The active ingredient may also be administered
13 parenterally in a sterile medium. The drug
14 depending on the vehicle and concentration used, can
15 either be suspended or dissolved in the vehicle.
16 Advantageously, adjuvants such as a local anesthetic,
17 preservative and buffering agents can be dissolved in
18 the vehicle.

19
20 For use in the treatment of rheumatoid arthritis the
21 compounds of this invention can be administered by
22 the oral route or by injection intra-articularly into
23 the affected joint. The daily dosage for a 70 kg
24 mammal will be in the range of 10 mgs to 1 gram of a
25 compound of general formula I.

26
27 The following examples illustrate the invention, but
28 are not intended to limit the scope in any way. The
29 following abbreviations have been used in the
30 Examples:-

31
32
33

- 1 DCC - Dicyclohexylcarbodiimide
2 DCM - Dichloromethane
3 DCU - Dicyclohexylurea
4 DIPE - Diisopropyl ether
5 DMF - N,N-dimethylformamide
6 HOBT - Hydroxybenztriazole
7 NMM - N-Methylmorpholine
8 TFA - Trifluoroacetic acid
9 THF - Tetrahydrofuran
10 WSCDI - N-(Dimethylaminoethyl)-N'-ethylcarbodiimide

11

12 Example 1

13

14 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)-
15 succinyl]-L-phenylalanine-N-methylamide

16

17

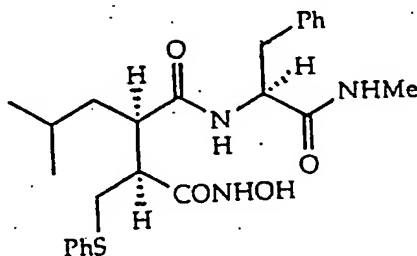
18

19

20

21

22



23 a) 2R-Bromo-5-methylpentanoic acid.

24

25 D-Leucine (100g, 0.76 mol) and potassium bromide
26 (317.5g, 2.67 mol) were dissolved in aqueous acid
27 (150ml concentrated sulphuric acid in 500ml of water).
28 The solution was cooled to -2° and sodium nitrite
29 (69.6g, 0.95 mol in water) was added over 1h taking
30 care to maintain the temperature between -1 and -2° .
31 After addition was complete the mixture was kept at 0°
32 for a further hour, then DCM was added and the mixture
33 stirred for a few minutes. The layers were separated

1 and the aqueous phase was washed with further portions
2 of DCM (5 x 250ml). The combined organic layers
3 were dried over magnesium sulphate then the solvent
4 removed to give the acid as a pale yellow oil (123.1g,
5 0.63 mol, 83%)

6

7 $[\alpha]_D = +38.0^\circ$ (c = 2, methanol)

8

9 δ_{H} (250 MHz, CDCl_3) 4.29 (1H, t, J = 6.5Hz,
10 BrCHCO_2H), 1.91 (2H, t, J = 7Hz, CHCH_2CH), 1.83 (1H, m,
11 Me_2CH), and 0.94 (6H, 2xd, J = 7Hz, $(\text{CH}_3)_2\text{CH}$)

12

13 b) tert-Butyl 2R-Bromo-5-methylpentanoate.

14

15 2R-Bromo-5-methylpentanoic acid (123g, 0.63 mol)
16 was dissolved in DCM (400ml) and the solution cooled
17 to -40° while isobutene was condensed in to roughly
18 double the volume. Maintaining the temperature at
19 -40° concentrated sulphuric acid (4ml) was added
20 dropwise. When the addition was complete the
21 reaction was allowed to warm to room temperature
22 overnight. The resultant solution was concentrated
23 to half the volume by removing the solvent at reduced
24 pressure, then the DCM was washed twice with an equal
25 volume of 10% sodium bicarbonate solution. The organic
26 layer was dried over magnesium sulphate and the
27 solvent removed under reduced pressure to leave the
28 title compound as a yellow oil (148.0g, 0.59 mol, 94%).

29

30 $[\alpha]_D = +23.0^\circ$ (c = 2, methanol)

31

32

33

1 δ_{H} (250 MHz, CDCl_3) 4.18 (1H, t, $J = 6.5\text{Hz}$,
2 BrCHCO_2H), 1.89 (2H, m, CHCH_2CH), 1.78 (1H, m, Me_2CH),
3 1.49 (9H, s, $(\text{CH}_3)_3\text{C}$) and 0.94 (6H, 2xd, $J = 7\text{Hz}$,
4 $(\text{CH}_3)_2\text{CH}$)

5

6 δ_{C} (63.9 MHz, CDCl_3) 167.0, 82.0, 46.3, 43.4,
7 27.6, 26.3, 22.2, and 21.6.

8

9 c) Benzyl (2-benzloxycarbonyl-3R-(tert-butoxycarbonyl)-
10 5-methylhexanoate.

11

12 Dibenzyl malonate (124.5g, 0.44 mol) was taken up in
13 dry DMF and potassium tert-butoxide (49.2g, 0.44
14 mol) was added portionwise with stirring and cooling.
15 When a homogeneous solution had formed it was cooled to
16 0° then tert-butyl-2R-bromo-5-methylpentanoate
17 (110.0g, 0.44 mol) in DMF (200 ml) was added dropwise
18 over 1h. When addition was complete the reaction was
19 transferred to a cold room at $<5^\circ$ and left for 4 days.
20 The reaction mixture was partitioned between ethyl
21 acetate and saturated ammonium chloride then the
22 aqueous layer extracted with further ethyl acetate
23 (4x500ml), drying and solvent removal left an oil
24 (228g) heavily contaminated with DMF. This oil was
25 taken into ether (1 litre) and washed with brine
26 (2x1l) then the organic layer dried (magnesium
27 sulphate), solvent removed under reduced pressure to
28 leave the desired material (179g) contaminated with a
29 small amount of dibenzyl malonate.

30

31 $[\alpha]_{\text{D}} = +22.5^\circ$ (c = 2, methanol)

32

33

1 δ_{H} (250 MHz, CDCl_3) 7.40 - 7.25 (10H, m, Aromatic
2 H), 5.14 (4H, 2xABq, CH_2Ph), 3.77 (1H, d, $J = 10\text{Hz}$,
3 $\text{BnO}_2\text{CCHCO}_2\text{Bn}$), 3.09 (1H, dt, $J = 10, 6\text{Hz}$,
4 $\text{CH}_2\text{CHCO}_2\text{tBu}$), 1.50 (3H, m, $\text{CH}_2 + \text{CHMe}_2$) 1.41 (9H, s,
5 $\text{C}(\text{CH}_3)_3$) and 0.88 (6H, 2xd, $J = 7\text{Hz}$).

6

7 d) [4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutyl-
8 succinyl]-L-phenylalanine-N-methylamide

9

10 Benzyl(2-benzyloxycarbonyl-5-methyl-3R-tert-butoxycarb-
11 onyl)-hexanoate (281.4g, 0.56 mol) was taken up in 5%
12 water in TFA (410 ml) and allowed to stand at 5°
13 overnight. After this time the TFA was evaporated
14 under reduced pressure then the residue partitioned
15 between DCM (1l) and brine (200ml). Solvent removal
16 left an oil which crystallised on standing (230g).

17

18 The crude acid from this reaction was dissolved in DMF
19 (1l), then HOBT (95.3g, 0.64 mol), NMM (64g, 0.64 mol)
20 and phenylalanine-N-methylamide (113.0g, 0.64 mol) were
21 added at room temperature. The mixture was cooled
22 to 0° before dropwise addition of DCC (131.0g, 0.64
23 mol) in THF (1l). This solution was stirred to room
24 temperature over the weekend. The precipitated DCU was
25 removed by filtration then the solvents were removed
26 from the filtrate under reduced pressure to leave an
27 oil. This oily residue was dissolved in ethyl acetate
28 then washed with 10% citric acid, 10% sodium
29 bicarbonate and saturated brine. The organic layer was
30 dried (magnesium sulphate), filtered then the solvent
31 removed under reduced pressure to give the title
32 compound as an oil (400g). This material was columned
33 on silica using gradient elution (0 - 50% ethyl

1 acetate in hexane) to remove impurities and separate
2 a small amount of the minor diastereoisomer. The
3 material from the column (195g) was recrystallised
4 from DIPE to give the title compound as a white
5 crystalline solid (140.2g, 0.25 mol, 47%)

6

7 m.p. 98 -99°

8 Analysis calculated for $C_{33}H_{38}N_2O_6$

9 Requires C 70.95 H 6.86 N 5.01

10 Found C 70.56 H 6.89 N 5.06

11

12 δ_H (250MHz, $CDCl_3$) 7.42 - 7.13 (15H, m, Aromatic
13 H), 6.58 (1H, d, $J=7.7$ Hz, CONH), 5.75 (1H, m,
14 CONHMe), 5.20 - 5.05 (4H, m, OCH_2Ph), 4.50 (1H, dt, $J=$
15 6.9, 7.7Hz, $CHCH_2Ph$), 3.79 (1H, d, $J=9.1$ Hz,
16 $CH(CO_2Bn)$), 3.15 - 2.91 (2H, m, CH_2Ph), 2.65 (3H, d, $J=$
17 4.8Hz, $CONHCH_3$), 1.52 (1H, m, $CHCH_2CH$), 1.32 (1H, m,
18 $CH(CH_3)$), 1.05 (1H, m, $CHCH_2CH$), and 0.74 (6H, 2xd, $J=$
19 6.5Hz, $CH(CH_3)_2$)

20

21 e) [4-Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-phenyl-
22 alanine-N-methylamide.

23

24 [4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-
25 L-phenylalanine-N-methylamide (29.6g, 53mmol) was taken
26 up in ethanol, ammonium formate (16.7g, 265mmol) added
27 followed by 10% palladium on charcoal (6g) as a
28 slurry in isopropyl alcohol. After 30 minutes at room
29 temperature the catalyst was removed by filtration,
30 then washed with ethanol to give a solution of the
31 crude diacid. To this was added piperidine (5.0g) and
32 the mixture stirred at room temperature for 15 minutes
33 before addition of aqueous formaldehyde (40%

1 solution, 25ml). After 18 hours at room temperature
2 the mixture was refluxed for 1 h. Solvents were
3 removed under reduced pressure and the residue
4 partitioned between ethyl acetate and citric acid.
5 The acid layer was extracted with further portions of
6 ethyl acetate (2x250ml), the combined organic layers
7 were extracted with potassium carbonate (3x200ml).
8 These base extracts were acidified to pH 4 and
9 re-extracted with DCM then the organic layer dried
10 over magnesium sulphate. Solvent removal
11 under reduced pressure gave the desired product as a
12 white solid (9.35g, 27.0mmol, 51%).

13

14 m.p. 149-151°C

15

16 δ_{H} (250MHz, CDCl_3) 8.37 (2H, d, $J=9.0\text{Hz}$, CONH),
17 7.39 (1H, m, CONHMe), 7.27 - 7.06 (5H, m, Aromatic
18 H), 6.40 (1H, s, $\text{CH}_2\text{CHCO}_2\text{H}$), 5.78 (1H, s, $\text{CH}_2\text{CHCO}_2\text{H}$),
19 4.93 (1H, q, $J=7\text{Hz}$, CHCH_2Ph), 3.92 (1H, m, CH_2CHCONH),
20 2.95 (2H, m, CH_2Ph), 2.71 (3H, d, $J=4.1\text{Hz}$, NHCH_3),
21 1.68 (1H, m), 1.45 (2H, m), and 0.86 (6H, 2xd, $J=$
22 5.8Hz, $\text{CH}(\text{CH}_3)_2$).

23

24 δ_{C} (63.9Hz, CDCl_3) 173.3, 172.8, 169.6, 139.1,
25 136.3, 129.2, 128.3, 127.0, 126.6, 54.4, 43.5, 41.4,
26 39.1, 26.2, 25.7, 22.5 and 22.4

27

28 f) [4-Hydroxy-2R-isobutyl-3S-(phenylthiomethyl)-
29 succinyl]-L-phenylalanine-N-methylamide

30

31 [4-Hydroxy-2R-isobuty-3-ethenylsuccinyl]-L-phenyl-
32 alanine-N-methylamide (15.0g, 44mmol) was dissolved in
33 thiophenol

1 (150ml) and the mixture stirred in the dark under
2 nitrogen at 60° for 2 days. Ether was added to the
3 cooled reaction mixture and the precipitated product
4 collected by filtration. The solid was washed with
5 large volumes of ether and dried under vacuum to give
6 the title compound (13.1g, 28.7mmol, 65%).

7

8 m.p. 199-201°C

9 Analysis calculated for C₂₅H₃₂N₂O₄S

10 Requires C 65.76 H 7.06 N 6.14 S 7.02

11 Found C 65.69 H 7.06 N 6.07 S 7.05

12

13 δ_{H} (250MHz, D₆-DMSO) 8.40 (1H, d, J= 9Hz, CONH),
14 7.82 (1H, m, CONHMe), 7.35 - 7.10 (7H, m, Aromatic
15 H), 7.04 (3H, m, Aromatic H), 4.62 (1H, m, CHCH₂Ph),
16 2.94 (1H, dd, J= 14,5Hz, CHCH₂Ph), 2.89 (1H, dd, J=
17 14,9Hz, CHCH₂Ph), 2.62 (3H, d, J= 4.5Hz, CONHCH₃), 2.41
18 (3H, m, 2xCH + CH₂SPh), 2.23 (1H, d, J= 12Hz, CH₂SPh),
19 1.43 (1H, m, CHCH₂CH), 1.30 (1H, bm, CH(CH₃)₂), 0.90
20 (1H, m, CHCH₂CH) and 0.78 (6H, 2xd, J= 6.5Hz, CH(CH₃)₂).

21

22 g) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthio-
23 methyl) succinyl]-L-phenylalanine-N-methylamide

24

25 [4-Hydroxy-2R-isobutyl-3S-(phenylthiomethyl)succinyl]-
26 L-phenylalanine-N-methylamide (16.8g, 37 mmol) and
27 HOBT (6.6g, 44 mmol) were dissolved in DCM / DMF
28 (4:1) and the mixture cooled to 0° before adding WSCDI
29 (8.5g, 44 mmol) and NMM (4.5g, 44 mmol). The mixture
30 was stirred at 0° for 1h to ensure complete formation
31 of the activated ester. Hydroxylamine hydrochloride
32 (3.8g, 55 mmol) and NMM (5.6g, 55 mmol) were dissolved
33 in DMF then this mixture added dropwise to the cooled

1 solution of the activated ester. After 1h the reaction
2 was poured into ether / water (1:1) whereupon the
3 desired product precipitated as white crystals. These
4 were collected by filtration, further washed with ether
5 and water then dried under vacuum at 50°. This
6 material was recrystallised from methanol / water (1:1)
7 to remove a trace of the minor diastereomer (9.03g,
8 19.2 mmol, 52%).

9

10 m.p. 227-229°C

11

12 $[\alpha]_D = -88^\circ$ (c = 10, methanol)

13

14 δ_{H} (250MHz, D₆-DMSO) 8.84 (1H, d, J= 1.5Hz, NHOH),
15 8.35 (1H, d, J= 8.7Hz, CONH), 7.87 (1H, m, CONHMe),
16 7.29 - 6.92 (11H, m, Aromatic H + NHOH), 4.60 (1H, m,
17 CHCH₂Ph), 2.94 (1H, dd, J= 13.5, 4.3, CHCH₂Ph), 2.77
18 (1H, dd, J= 13.5, 10, CHCH₂Ph), 2.60 (3H, d, J= 4.6Hz),
19 2.53 (1H, m), 2.41 (1H, m), 2.20 (1H, dd, J=
20 13.4, 2.2Hz, CH₂SPh), 2.09 (1H, dd, J=13.4, 2.4Hz,
21 CH₂SPh), 1.38 (2H, m, CHMe₂ + CHCH₂CH), 0.88 (1H,
22 m, CHCH₂CH), 0.82 (3H, d, J= 6.4Hz, CH(CH₃)₂), and 0.74
23 (3H, d, J+ 6.4Hz, CH(CH₃)₂).

24

25 δ_{C} (63.9MHz, D₆-DMSO) 172.9, 171.6, 166.3, 138.1,
26 136.7, 129.1, 128.9, 128.0, 127.3, 126.4, 125.2, 54.2,
27 46.4, 46.0, 37.7, 32.4, 25.6, 25.2, 24.2, and 21.7.

28

29

30

31

32

33

1 Example 2

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthiometh-
4 yl) succinyl]-L-phenylalanine-N-methylamide

5

6

7

8

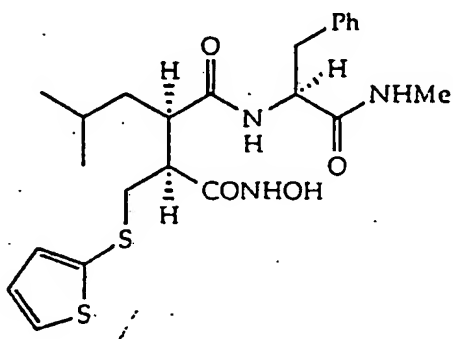
9

10

11

12

13

14 a) [4-N-Hydroxy-2R-isobutyl-3S-(thiophenylthiomethyl)
15 succinyl]-L-phenylalanine-N-methylamide

16

17 The title compound was prepared from
18 [4-Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-phenyl-
19 alanine-N-methylamide (400mg, 1.16mmol) by the method
20 described in example 1f, substituting thiophenethiol in
21 the place of thiophenol to give a material (320mg,
22 0.73mmol, 63%) with the following characteristics.

23

24 m.p. 184-186°C

25

26 δ_{H} (250MHz, D_6 -DMSO) 8.29 (1H, d, $J = 8.1\text{Hz}$, CONH),
27 7.84 (1H, m, CONHMe), 7.57 (1H, d, $J = 5.1\text{Hz}$,
28 Thiophene H), 5H, m, Aromatic H), 7.00 (2H, m,
29 Thiophene H), 4.50 (1H, m, CHCH_2Ph), 2.91 (1H, m,
30 CHCH_2Ph), 2.75 (1H, m, CHCH_2Ph), 2.56 (3H, d, $J =$
31 4.0Hz, CONHCH₃), 2.34 (3H, m), 1.99 (1H, d, $J = 9.3\text{Hz}$,

32

33

1 CH_2SHet), 1.42 (1H, m, CHCH_2CH), 1.29 (1H, bm,
2 $\text{CH}(\text{CH}_3)_2$), 0.87 (1H, m, CHCH_2CH), 0.79 (3H, d, J=
3 6.4Hz, $\text{CH}(\text{CH}_3)_2$), and 0.72 (3H, d, J= 6.4Hz, $\text{CH}(\text{CH}_3)_2$).
4

5 b) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthio-
6 methyl)succinyl]-L-phenylalanine-N-methylamide
7

8 Prepared by the method described in example 1g to
9 give material with the following characteristics
10

11 m.p. 236-238°C
12

13 Analysis calculated for $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_4\text{S}_2$

14 Requires C 57.84 H 6.54 N 8.80

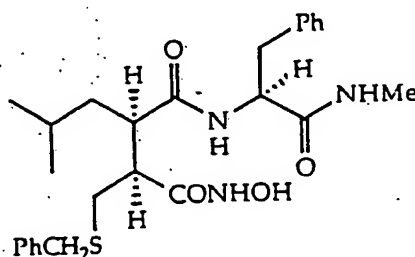
15 Found C 57.64 H 6.48 N 8.85
16

17 δ_{H} (250MHz, D_6 -DMSO) 8.80 (1H, s, CONHOH), 8.08
18 (1H, d, J=8Hz, CONH), 7.52 (1H, m, CONHMe), 7.32 (1H,
19 dd, J= 4.6,2.9Hz, Thiophene H), 7.17 - 6.95 (5H, m,
20 Aromatic H), 6.89 (2H, m, Thiophene H), 4.46 (1H,
21 m, CHCH_2Ph), 2.89 (1H, dd, J=13.6,4.4Hz, CHCH_2Ph), 2.72
22 (1H, dd, J= 13.6,10.5Hz, CHCH_2Ph), 2.54 (3H, d, J=
23 4.3Hz, CONHCH_3), 2.46 (1H, d, J= 12.1Hz, CH_2S), 2.35
24 (1H, bt, J= 10.2Hz), 2.14 (1H, bt, J= 10.2Hz), 1.98
25 (1H, dd, J=12.7,2.5Hz, CHCH_2Ph), 1.35 (1H, bt, J=
26 11.4Hz, CHCH_2CH), 1.22 (1H, bm, $\text{CH}(\text{CH}_3)_2$), 0.86 (1H,
27 bt, J=12.6Hz, CHCH_2CH), 0.74 (3H, d, J= 6.3Hz,
28 $\text{CH}(\text{CH}_3)_2$), and 0.68 (3H, d, J= 6.4Hz, $\text{CH}(\text{CH}_3)_2$).
29

30 δ_{C} (63.9MHz, D_6 -DMSO) 172.5, 171.6, 166.1, 138.0,
31 133.8, 132.7, 129.4, 129.2, 128.1, 127.8, 126.5, 54.2,
32 46.2, 46.0, 38.5, 37.6, 25.8, 25.2, 24.2, and 21.7.
33

Example 3

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(benzylthiomethyl) succinyl]-L-phenylalanine-N-methylamide



Prepared by the method described in example 1g to give material with the following characteristics

m.p. °

Analysis calculated for $C_{27}H_{37}N_3O_5S \cdot 0.5H_2O$

Requires C 61.81 H 7.30 N 8.00

Found C 61.85 H 7.15 N 7.45

δ_{H} (250MHz, D_6 -DMSO) 8.40 (1H, s, CONHOH), 8.22 (1H, m, NHMe), 7.20 (5H, m, Aromatic H), 6.58 (4H, m), 4.10 (1H, m, CHCH₂Ph), 3.22 (3H, s, OCH₃), 3.04 - 2.45 (4H, m, 2xCH₂Ar), 2.42 (3H, d, J= 6Hz, NHCH₃), 2.32 - 2.08 (4H, m), 0.78 (2H, m, CHCH₂CH), and 0.40 - 0.18 (7H, m, (CH₃)₂CH).

1 Example 4

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(acetylthiomethyl)
4 succinyl]-L-phenylalanine-N-methylamide

5

6

7

8

9

10

11

12

13 Prepared by the method described in example 1g to
14 give material with the following characteristics

15

16 m.p. 226-227°C

17

18 Analysis calculated for $C_{21}H_{31}N_3O_5S \cdot H_2O$

19 Requires C 55.37 H 7.30 N 9.22

20 Found C 55.57 H 6.99 N 9.53

21

22 δ_H (250MHz, D_6 -DMSO) 8.84 (1H, s, $NHOH$), 8.36 (1H,
23 d, $J=8Hz$, $CONH$), 7.80 (1H, d, $J=6Hz$, $NHMe$), 7.20 (7h,
24 m, Aromatic H), 4.58 (1H, m, $CHCH_2Ph$), 3.16 - 2.62
25 (2H, m, $CHCH_2Ph$), 2.54 (3H, d, $J=4Hz$, $NHCH_3$), 2.22
26 (3H, s, CH_3COS), 2.36 - 2.10 (4H, m, $CHCHCH_2S$), 1.36
27 (2H, m, $CHCH_2CH$), and 0.98 - 0.66 (7H, m, $CH(CH_3)_2$).

28

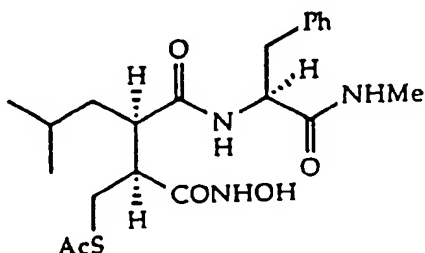
29

30

31

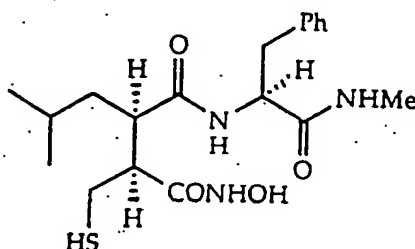
32

33



1 Example 5

2
3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiolmethyl)
4 succinyl]-L-phenylalanine-N-methylamide



12 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(acetylthiomethyl)
13 succinyl]-L-phenylalanine-N-methylamide (30mg,
14 0.06mmol) was stirred in methanol (3ml) with
15 methylamine (1ml methanolic solution) at room
16 temperature. After 30 minutes the crystalline
17 product (20mg, 0.05mmol, 74%) was filtered off and
18 dried.

19
20 m.p. 234°C

21 Analysis calculated for $C_{19}H_{39}N_3O_4S \cdot 1.5H_2O$

22 Requires C 54.10 H 7.63 N 9.94 S 7.60

23 Found C 54.28 H 7.16 N 10.43 S 7.80

24
25 δ_{H} (250MHz, D_6 -DMSO) 8.28 (1H, d, $J=9\text{Hz}$, NHOH),
26 7.80 (1H, m, NHMe), 7.22 (5H, m, Aromatic H), 4.60 (1H,
27 m, CHCH_2Ph), 3.08 - 2.56 (2H, m, CHCH_2Ph), 2.50 (3H, d,
28 $J=4\text{Hz}$, NHCH_3), 2.40 - 2.02 (4H, m, CHCHCH_2SH), 1.44
29 - 1.22 (2H, m, CHCH_2CH) and 0.98 - 0.72 (7H, m,
30 $\text{CH}(\text{CH}_3)_2$).

31

32

33

1 Example 6

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(benzoylthiomethyl)-
4 succinyl]-L-phenylalanine-N-methylamide

5

6

7

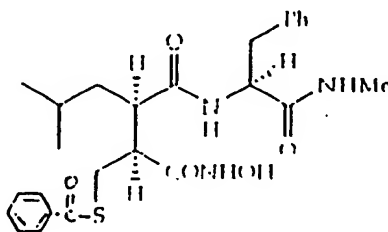
8

9

10

11

12



13 The title compound was prepared by the method described
14 in Example 1g to give material with the following
15 characteristics

16

17 m.p. 227 - 228°

18 Analysis calculated for C₂₁H₃₁N₃O₅S

19 Requires C 62.50 H 6.66 N 8.41

20 Found C 62.32 H 6.67 N 8.40

21

22 δ_{H} (250 MHz, CDCl₃:D₆DMSO (1:1)) 8.82 (1H, s,
23 NHOH), 8.25 (1H, d, J=8.4Hz, NHOH), 7.87 (2H, dd,
24 J=8.5, 1.1Hz), 7.60 (2H, m, Ar-H and CONH), 7.50 (2H,
25 t, J=8.2Hz), 7.28 (2H, d, J=8.4Hz), 7.16 (2H, t,
26 J=7.2Hz), 7.04 (1H, t, J=8.5Hz), 4.65 (1H, m, CHCH₂Ph),
27 3.06 (1H, dd, J=14.1, 5.0Hz, CHCH₂Ph), 2.90 (1H, dd,
28 J=13.9, 10Hz, CHCH₂Ph), 2.73 (2H, m SCH₂Ph), 2.65 (3H,
29 d, J=4.7Hz, NHMe), 2.33 (1H, dt, J=11.0, 4.7Hz), 1.51
30 (1H, t, J=7Hz, CH₂CHMe₂), 1.24 (1H, m, CHMe₂), 0.97
31 (1H, t, J=7Hz, CH₂CHMe₂), 0.84 (3H, d, J=6.5Hz, CHMe₂)
32 and 0.79 (3H, d, J=6.5Hz, CHMe₂).

33

1 Example 7

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(pivaloylthiomethyl)
4 succinyl]-L-phenylalanine-N-methylamide

5

6

7

8

9

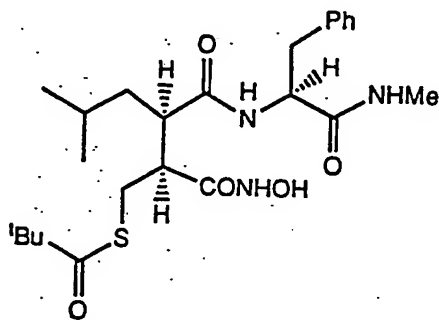
10

11

12

13

14



15 [4-Hydroxy-2R-isobutyl-3S-(pivaloylthiomethyl)
16 succinyl]-L-phenylalanine-N-methylamide (0.8g, 1.7
17 mmol) and HOBt (0.31g, 2.1 mmol) were dissolved in 1:1
18 DCM/DMF and the mixture cooled to 0°C before adding
19 WSDCI (0.4g, 2.1mmol) and NMM (0.21g, 2.1mmol). The
20 mixture was stirred at 0°C for 1h to ensure complete
21 formation of the activated ester. Hydroxylamine
22 hydrochloride (0.18g, 2.6mmol) and NMM (0.26g, 2.6mmol)
23 were dissolved in DMF then this mixture was added
24 dropwise to the cooled solution of the activated ester.
25 After 1h the reaction was poured into ether/water (1:1)
26 whereupon the desired product precipitated as white
27 crystals. These were collected by filtration, further
28 washed with ether and water, then dried under vacuum at
29 50°C. This material was recrystallised from
30 methanol/water (1:1) to remove a trace of the minor
31 diastereomer (0.38g, 0.7mmol, 45%).

32

33 m.p. 225°C

1 $[\alpha]_D = -3.5^\circ$ (c=2, methanol)

2

3 Analysis calculated for $C_{24}H_{39}N_3O_5S \cdot 0.5 H_2O$

4 Requires: C58.99 H7.84 N8.60

5 Found: C58.96 H7.63 N8.55

6

7 δ_H (250MHz, D_6 -DMSO) 8.81 (1H, s, $J = 1.5$ Hz, $NH\bar{O}H$),
8 8.30 (1H, d, $J=8$ Hz, $CONH$), 7.78 (1H, d, $J=6$ Hz, $CONHMe$),
9 7.27-7.03 (5H, m, aromatic H), 4.54 (1H, m, $CHCH_2Ph$),
10 2.94 (1H, dd, $J = 12, 5$ Hz, $CHCH_2Ph$), 2.79 (1H, dd, $J =$
11 13, 10Hz, $CHCH_2Ph$) 2.56 (3H, d, $J = 4.5$ Hz, $NHCH_3$), 2.44
12 (2H, m), 2.20 (1H, dd, $J = 13, 3$ Hz, CH_2S), 2.07 (1H,
13 dt), 1.36 (2H, m), 1.13 (9H, s, $C(CH_3)_3$), 0.87 (1H, m,
14 $CH_2CH(CH_3)_2$), 0.79 (3H, d, $J = 6$ Hz, $CH(CH_3)_2$), and 0.74
15 (3H, d, $J = 6$ Hz, $CH(CH_3)_2$).

16

17 δ_C (63.9MHz, D_6 -DMSO) 172.55, 171.59, 168.24,
18 138.03, 129.18, 128.00, 126.24, 54.21, 46.48, 45.84,
19 45.55, 37.61, 28.30, 27.13, 25.64, 25.25, 24.24, and
20 21.63.

21

22 Example 8

23

24 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)
25 succinyl]-L-phenylalanine-N-methylamide sodium salt

26

27

28

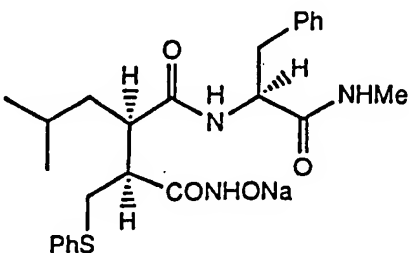
29

30

31

32

33



[4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide (0.2g, 0.4 mmol) was dissolved in 20ml of methanol and 1eq of 0.1N NaOH(aq) added. The solvent was removed in vacuo and the residue dissolved in water and freeze-dried (0.21g, 0.4 mmol, 100%).

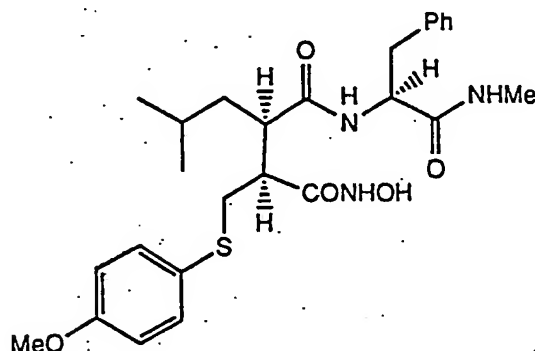
m.p. 184°C

$[\alpha]_D = -7.7^\circ$ (c=2, methanol)

δ_H (250MHz, D_6 -DMSO) 8.62 (1H, s, $J = 1.5\text{Hz}$, NHOH), 8.28 (1H, d, $J = 8\text{Hz}$, CONH), 7.26 - 7.04 (10H, m, aromatic H), 4.43 (1H, m, CHCH_2Ph), 3.00 (1H, dd, $J = 14, 4\text{Hz}$, CHCH_2Ph), 2.84 (1H, dd, $J = 14, 10\text{Hz}$, CHCH_2Ph), 2.55 (3H, d, $J = 4.5\text{Hz}$, NHCH_3), 2.46 (3H, m), 2.21 (1H, m), 1.39 (1H, m), 1.14 (1H, m), 1.00 (1H, m), and 0.70 (6H, d, $J = 5.7\text{Hz}$)

Example 9

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenylthiomethyl)]



1 succinyl]-L-phenylalanine-N-methylamide[4-Hydroxy-2R-
2 isobutyl-3S-(4-methoxyphenylthiomethyl)succinyl]-L-
3 phenylalanine-N-methylamide (0.5g, 1 mmol) and HOBt
4 (0.18g, 1.2 mmol) were dissolved in 1:1 DCM/DMF and the
5 mixture cooled to 0°C before adding WSDCI (0.23g,
6 1.2mmol) and NMM (0.12g, 1.2mmol). The mixture was
7 stirred at 0°C for 1h to ensure complete formation of
8 the activated ester. Hydroxylamine hydrochloride (0.1g,
9 1.5mmol) and NMM (0.15g, 1.5mmol) were dissolved in DMF
10 then this mixture was added dropwise to the cooled
11 solution of the activated ester. After 1h the reaction
12 was poured into ether/water (1:1) whereupon the desired
13 product precipitated as white crystals. These were
14 collected by filtration, further washed with ether and
15 water, then dried under vacuum at 50°C. This material
16 was recrystallised from methanol/water (1:1) to remove
17 a trace of the minor diastereomer (0.36g, 0.7mmol,
18 72%).

19 m.p. 225°C

20
21 [alpha]_D = +8° (c=0.5, methanol)

22
23 Analysis calculated for C₂₆H₃₅N₃O₅S

24 Requires: C62.25 H7.04 N8.38

25 Found: C62.43 H7.09 N8.37

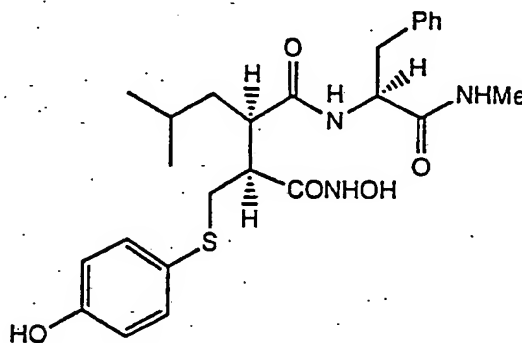
26
27 delta_H (250MHz, D₆-DMSO) 8.83 (1H, s, J = 1.5Hz, NHOH),
28 8.28 (1H, d, J = 8Hz, CONH), 7.83 (1H, d, J = 6Hz,
29 CONHMe), 7.28 - 6.86 (9H, m, aromatic H), 4.52 (1H, m,
30 CHCH₂Ph), 3.73 (3H, s, OCH3), 2.91 (1H, dd, J = 14,4Hz,
31 CHCH₂Ph), 2.75 (1H, dd, J = 14,10Hz, CHCH₂Ph), 2.57
32 (3H, d, J = 4.5Hz, NHCH₃), 2.50 - 2.34 (2H,m), 2.16 -
33

1 1.99 (2H, m, CH₂CH(CH₃)₂) 1.36 (2H, m), 0.88 (1H, m,
2 CH₂CH(CH₃)₂), 0.80 (3H, d, J = 6Hz, CH(CH₃)₂), and 0.73
3 (3H, d, J = 6Hz, CH(CH₃)₂).

4
5 delta_C (63.9MHz, D₆-DMSO) 172.79, 171.62, 168.39,
6 138.14, 131.34, 129.19, 128.00, 126.44, 114.59, 55.32,
7 54.20, 38.68, 25.63, 25.17, 24.26, and 21.70.

8
9 Example 10

10
11 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenyl-
12 thiomethyl) succinyl]-L-phenylalanine-N-methylamide



23 [4-Hydroxy-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)
24 succinyl]-L-phenylalanine-N-methylamide (0.4g, 0.8
25 mmol) and HOBT (0.15g, 1.0 mmol) were dissolved in 1:1
26 DCM/DMF and the mixture cooled to 0°C before adding
27 WSDCI (0.20g, 1.0mmol) and NMM (0.1g, 1.0mmol). The
28 mixture was stirred at 0°C for 1h to ensure complete
29 formation of the activated ester. Hydroxylamine
30 hydrochloride (0.09g, 1.3mmol) and NMM (0.13g, 1.3mmol)
31 were dissolved in DMF then this mixture was added
32 dropwise to the cooled solution of the activated ester.
33 After 1h the reaction was poured into ether/water (1:1)

1 whereupon the desired product precipitated as white
2 crystals. These were collected by filtration, further
3 washed with ether and water, then dried under vacuum at
4 50°C. This material was recrystallised from
5 methanol/water (1:1) to remove a trace of the minor
6 diastereomer (0.13g, 0.2mmol, 31%).

7

8 m.p. 216°C

9

10 $[\alpha]_D = -65^\circ$ (c=0.5, methanol)

11

12 Analysis calculated for $C_{25}H_{33}N_3O_5S$

13 Requires: C61.58 H6.82 N8.62

14 Found: C61.43 H6.81 N8.08

15

16 δ_{H} (250MHz, D_6 -DMSO) 8.82 (1H, s, $J = 1.5\text{Hz}$, NHOH),
17 8.26 (1H, d, $J = 8\text{Hz}$, CONH), 7.81 (1H, d, $J = 6\text{Hz}$,
18 CONHMe), 7.27 - 6.64 (9H, m, aromatic H), 4.49 (1H, m,
19 CHCH_2Ph), 2.90 (1H, dd, $J=14,4\text{Hz}$, CHCH_2Ph), 2.74 (1H,
20 dd, $J=14,10\text{Hz}$, CHCH_2Ph), 2.57 (3H, d, $J = 4.5\text{Hz}$,
21 NHCH_3), 2.54 - 2.29 (2H, m), 2.14 - 1.98 (2H, m,
22 $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 1.35 (2H, m), 0.88 (1H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$),
23 0.80 (3H, d, $J = 6\text{Hz}$, $\text{CH}(\text{CH}_3)_2$), and 0.73 (3H, d, $J =$
24 6Hz , $\text{CH}(\text{CH}_3)_2$).

25

26 δ_{C} (63.9MHz, D_6 -DMSO) 172.81, 171.66, 168.46,
27 156.50, 133.02, 132.17, 129.17, 128.02, 126.44, 124.17,
28 116.00, 54.20, 46.35, 46.13, 37.59, 35.40, 25.62,
29 25.16, 24.27, and 21.69.

30

31

32

33

1 Example 11

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thiophenethio-
 4 methyl)succinyl]-L-phenylalanine-N-methylamide sodium
 5 salt

6

7

8

9

10

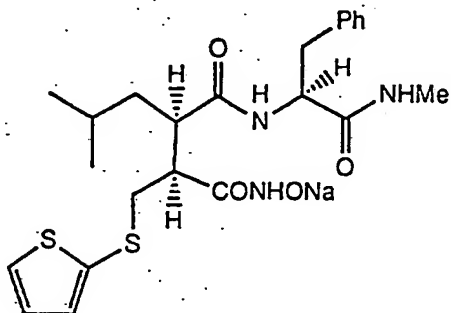
11

12

13

14

15



16 [4-Hydroxyamino)-2R-isobutyl-3S-(2-thiophenethiomethyl)
 17 succinyl]-L-phenylalanine-N-methylamide (0.2g, 0.4
 18 mmol) was dissolved in 20ml of methanol and 1eq of 0.1N
 19 NaOH(aq) added. The solvent was removed in vacuo and
 20 the residue dissolved in water and freeze-dried
 21 (0.21g, 0.4 mmol, 100%).

22

23 m.p. 170°C

24

25 $[\alpha]_D = -67^\circ$ (c=1, methanol)

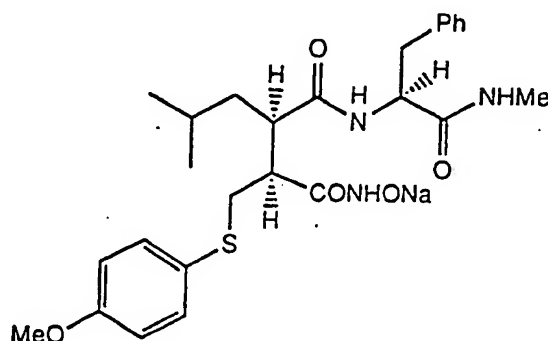
26

27 δ_H (250MHz, d_6 -DMSO), 7.51 (1H, d), 7.19 - 6.97
 28 (8H, m, aromatic H), 4.32 (1H, m, $\underline{CHCH_2Ph}$), 3.00 (1H,
 29 dd, $J = 14, 4\text{Hz}$, $\underline{CHCH_2Ph}$), 2.84 (1H, dd, $J = 14, 10\text{Hz}$,
 30 $\underline{CHCH_2Ph}$) 2.53 (3H, d, $J = 4.5\text{Hz}$, $\underline{NHCH_3}$), 2.46 2.19 (3H,
 31 m), 1.37 (1H, m), 1.09 (1H, m), 0.93 (1H, m), and 0.67
 32 (6H, m)

33

1 Example 12

2
3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenyl-
4 thiomethyl)succinyl]-L-phenylalanine-N-methylamide
5 sodium salt



16
17 [4-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenylthio-
18 methyl)succinyl]-L-phenylalanine-N-methylamide (0.1g,
19 0.2 mmol) was dissolved in 20ml of methanol and 1eq of
20 0.1N NaOH(aq) added. The solvent was removed in vacuo
21 and the residue dissolved in water and freeze-dried
22 (0.1g, 0.2 mmol, 100%).

23
24 m.p. 174°C

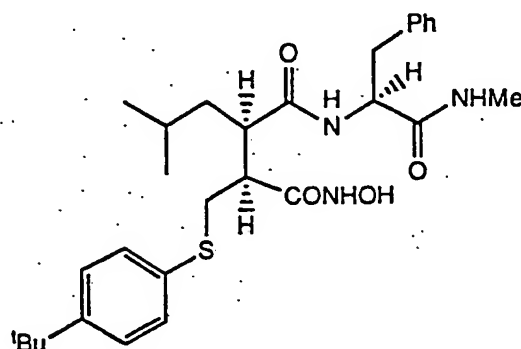
25
26 $[\alpha]_D = -58^\circ$ (c=1, methanol)

27
28 δ_H (250MHz, D_6 -DMSO δ) 7.26 - 7.04 (10H, m, aromatic
29 H), 4.31 (1H, m, $CHCH_2Ph$), 3.73 (3H, s, OCH_3), 3.25 -
30 2.72 (2H, m, $CHCH_2Ph$), 2.50 (3H, s, $NHCH_3$), 2.36 (1H,
31 m), 2.15 (1H, m), 1.37 (1H, m), 0.95 (1H, m), and 0.69
32 (6H, d, $CHCH_2(CH_3)_2$).

33

Example 13

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-tertbutylphenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide



[4-Hydroxy-2R-isobutyl-3S-(4-tertbutylphenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide (5.0g, 10 mmol) and HOBt (1.76g, 12 mmol) were dissolved in 1:1 DCM/DMF and the mixture cooled to 0°C before adding WSDCI (2.3g, 12mmol) and NMM (1.2g, 12mmol). The mixture was stirred at 0°C for 1h to ensure complete formation of the activated ester. Hydroxylamine hydrochloride (1.0g, 15mmol) and NMM (1.2g, 15mmol) were dissolved in DMF then this mixture was added dropwise to the cooled solution of the activated ester. After 1h the reaction was poured into ether/water (1:1) whereupon the desired product precipitated as white crystals. These were collected by filtration, further washed with ether and water, then dried under vacuum at 50°C. This material was repeatedly recrystallised from methanol/water (1:1) to remove a trace of the minor diastereomer (0.7g, 1.3mmol, 14%).

1 M.p. 188.5 -190°C

2

3 Analysis calculated for $C_{29}H_{41}N_3O_4S$

4 Requires: C66.00 H7.83 N7.96

5 Found: C65.80 H7.81 N7.76

6

7 δ_{H} (250MHz, D_6 -DMSO) 8.83 (1H, s, NHOH), 8.33 (1H,
8 d, $J = 8\text{Hz}$, CONH), 7.86 (1H, d, $J = 6\text{Hz}$, CONHMe), 7.28
9 - 6.90 (9H, m, aromatic H), 4.60 (1H, m, CHCH_2Ph), 2.94
10 (1H, dd, $J = 14, 4\text{Hz}$, CHCH_2Ph), 2.77 (1H, dd, $J =$
11 $14, 10\text{Hz}$, CHCH_2Ph), 2.58 (3H, d, $J = 4.5\text{Hz}$, NHCH_3), 2.55
12 - 2.37 (2H, m), 2.22 - 2.08 (2H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 1.37
13 (2H, m), 1.26 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.88 (1H, m,
14 $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.81 (3H, d, $J = 6\text{Hz}$, $\text{CH}(\text{CH}_3)_2$), and 0.74
15 (3H, d, $J = 6\text{Hz}$, $\text{CH}(\text{CH}_3)_2$).

16

17 δ_{C} (63.9MHz, D_6 -DMSO) 172.88, 171.59, 168.34,
18 147.87, 138.10, 133.09, 129.13, 127.95, 127.45, 126.36,
19 125.70, 54.19, 54.20, 46.38, 46.06, 37.70, 34.20, 32.79
20 31.24, 25.64, 25.19, 24.25, and 21.72.

21

22 Example 14

23

24 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2,4-
25 dimethylphenylthiomethyl)succinyl]-L-phenylalanine-N-
26 methylamide

27

28

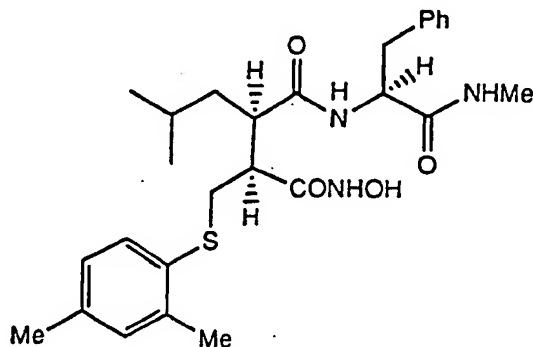
29

30

31

32

33



[4-Hydroxy-2R-isobutyl-3S-(2,4-dimethylphenylthio-methyl)succinyl]-L-phenylalanine-N-methylamide (1.8g, 3.7 mmol) and HOBT (0.67g, 12 mmol) were dissolved in 1:1 DCM/DMF and the mixture cooled to 0°C before adding WSDCI (0.86g, 4.5mmol) and NMM (0.45g, 4.5mmol). The mixture was stirred at 0°C for 1h to ensure complete formation of the activated ester. Hydroxylamine hydrochloride (0.39g, 5.6mmol) and NMM (0.56g, 5.6mmol) were dissolved in DMF then this mixture was added dropwise to the cooled solution of the activated ester. After 1h the reaction was poured into ether/water (1:1) whereupon the desired product precipitated as white crystals. These were collected by filtration, further washed with ether and water, then dried under vacuum at 50°C. This material was repeatedly recrystallised from methanol/water (1:1) to remove a trace of the minor diastereomer (1.08g, 2.2mmol, 58%).

m.p. 226°C (dec.)

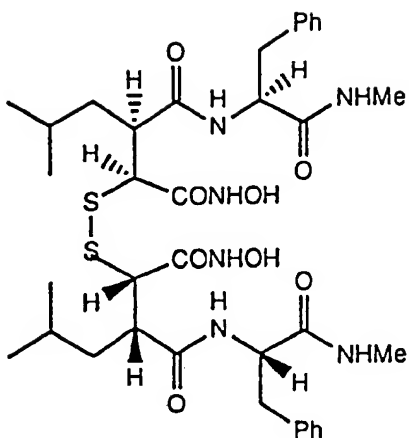
Analysis calculated for $C_{27}H_{37}N_3O_4S$

Requires: C64.90 H7.46 N8.41

Found: C65.15 H7.48 N8.40

δ_H (250MHz, D_6 -DMSO) 8.83 (1H, s, $NHOH$), 8.32 (1H, d, $J = 8Hz$, $CONH$), 7.85 (1H, d, $J = 6Hz$, $CONHMe$), 7.30 - 6.71 (9H, m, aromatic H), 4.56 (1H, m, $CHCH_2Ph$), 2.91 (1H, dd, $J = 14,4Hz$, $CHCH_2Ph$), 2.76 (1H, dd, $J = 14,10Hz$, $CHCH_2Ph$), 2.57 (3H, d, $J = 4.5Hz$, $NHCH_3$), 2.53 - 2.38 (2H, m), 2.23 (3H, s, $C_6H_5(CH_3)_2$), 2.13 (3H, s, $C_6H_5(CH_3)$), 1.30 (2H, m), 0.89 (1H, m, $CH_2CH(CH_3)_2$), 0.81 (3H, d, $J = 6Hz$, $CH(CH_3)_2$), and 0.74 (3H, d, $J = 6Hz$, $CH(CH_3)_2$).

1 Example 15

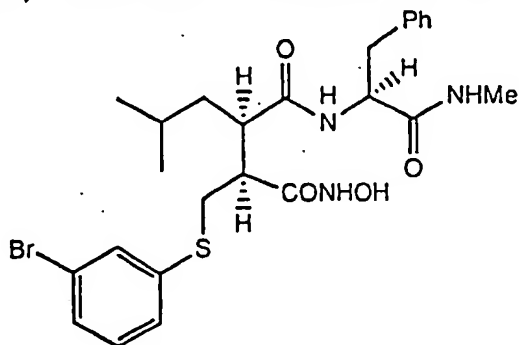


13 [4-(N-Hydroxyamino-2R-isobutyl-3S-(acetylthiomethyl)
14 succinyl]-L-phenylalanine-N-methylamide (1.0g, 2.4
15 mmol) was dissolved in 750ml methanol and 350ml pH 7
16 buffer added. Left to stand overnight and solvent
17 removed in vacuo to 2/3 volume, left to crystallise for
18 a further two hours. Filtered and dried to give 0.87g
19 off-white crystals

20
21 Analysis calculated for $C_{38}H_{56}N_6O_8S_2 \cdot 1.9H_2O$
22 Requires: C55.34 H6.93 N9.88
23 Found: C55.44 H7.32 N10.21
24

25 Example 16

26
27 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-bromophenyl-
28 thiomethyl) succinyl]-L-phenylalanine-N-methylamide



Prepared by the method described in example 1g to give material with the following characteristics.

m.p. 225 -229°C

$[\alpha]_D = -164.8^\circ$

Analysis calculated for $C_{25}H_{32}BrN_3O_4S$

Requires: C54.40 H5.89 N7.40

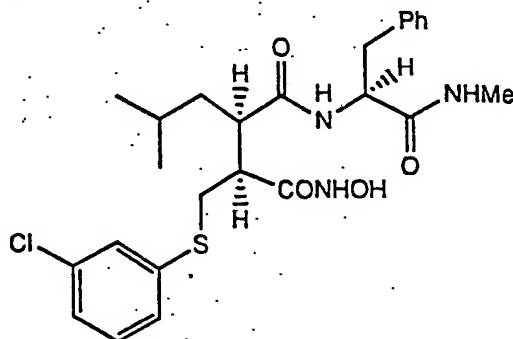
Found: C54.54 H5.86 N7.63

δ_H (250MHz, D_6 -DMSO) 8.83 (1H, s, NHOH), 8.35 (1H, d, $J = 8\text{Hz}$, CONH), 7.90 (1H, q, $J = 6\text{Hz}$, CONHMe), 7.35 - 6.87 (9H, m, aromatic H), 4.64 (1H, m, $CHCH_2Ph$), 2.94 (1H, dd, $J = 14, 4\text{Hz}$, $CHCH_2Ph$), 2.76 (1H, t, $J = 13\text{Hz}$, $CHCH_2Ph$) 2.60 (3H, d, $J = 5\text{Hz}$, $NHCH_3$), 2.55 - 2.35 (2H, m, CH_2S), 2.15 (1H, t, $J = 10\text{Hz}$, $CHCO$), 2.01 (1H, d, $J = 11.5\text{Hz}$, $CHCO$), 1.37 (2H, m), 0.88 (1H, m, $CH_2CH(CH_3)_2$), 0.81 (3H, d, $J = 6\text{Hz}$, $CH(CH_3)_2$), and 0.74 (3H, d, $J = 6\text{Hz}$, $CH(CH_3)_2$).

δ_C (63.9MHz, D_6 -DMSO) 173.0, 171.0, 168.8, 139.8, 138.0, 130.5, 129.0, 128.5, 127.5, 125.8, 125.5, 54.2, 46.0, 45.5, 38.0, 31.5, 25.5, 25.2, 24.7, and 21.0.

Example 17

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-chlorophenylthio-methyl) succinyl]-L-phenylalanine-N-methylamide



1 Prepared by the method described in example 1g to give
2 material with the following characteristics.

3
4 m.p. 231-234°C

5
6 $[\alpha]_D = -96.5^\circ$

7
8 Analysis calculated for $C_{25}H_{32}ClN_3O_4S$

9 Requires: C59.34 H6.37 N8.30

10 Found: C59.51 H6.43 N8.24

11
12 δ_H (250MHz, D_6 -DMSO) 8.85 (1H, s, NH_{OH}), 8.37 (1H,
13 d, $J = 8.5\text{Hz}$, $CONH$), 7.90 (1H, m, $CONHMe$), 7.30 - 6.88
14 (9H, m, aromatic H), 4.66 (1H, m, $CHCH_2Ph$), 2.96 (1H,
15 bd, $J = 14\text{Hz}$, $CHCH_2Ph$), 2.76 (1H, bt, $J = 13\text{Hz}$,
16 $CHCH_2Ph$) 2.60 (3H, d, $J = 5\text{Hz}$, $NHCH_3$), 2.55 - 2.40 (2H,
17 m, CH_2S), 2.16 (1H, m, $CHCO$), 2.01 (1H, d, $J = 14\text{Hz}$,
18 $CHCO$), 1.37 (2H, m), 0.91 (1H, m, $CH_2CH(CH_3)_2$), 0.81
19 (3H, d, $J = 6\text{Hz}$, $CH(CH_3)_2$), and 0.74 (3H, d, $J =$
20 6Hz , $CH(CH_3)_2$).

21
22 δ_C (63.9MHz, D_6 -DMSO) 172.7, 171.6, 168.1, 139.2,
23 138.1, 130.3, 129.2, 127.9, 126.2, 125.9, 125.5, 125.0,
24 54.1, 46.3, 45.8, 37.8, 32.0, 25.7, 25.2, 24.2, and
25 21.7.

26

27

28

29

30

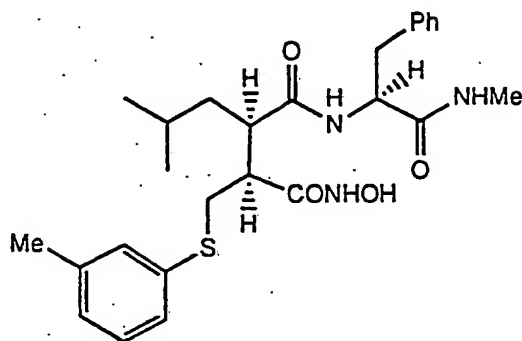
31

32

33

1 Example 18

2
3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-
4 methylphenylthiomethyl) succinyl]-L-phenylalanine-N-
5 methylamide



15 Prepared by the method described in example 1g to give
16 material with the following characteristics.

17
18 Analysis calculated for $C_{26}H_{35}N_3O_4S$

19 Requires: C64.30 H7.26 N8.65

20 Found: C63.81 H7.21 N8.48

21
22 δ_H (250MHz, D_6 -DMSO) 8.83 (1H, s, NH_{OH}), 8.35 (1H,
23 d, $J = 8.5\text{Hz}$, $CONH$), 7.86 (1H, m, $CONHMe$), 7.28 - 6.77
24 (9H, m, aromatic H), 4.66 (1H, m, $CHCH_2Ph$), 2.96 (1H,
25 dd, $J = 14, 4\text{Hz}$, $CHCH_2Ph$), 2.80 (1H, bt, $J = 13\text{Hz}$,
26 $CHCH_2Ph$) 2.59 (3H, d, $J = 5\text{Hz}$, $NHCH_3$), 2.55 - 2.37 (2H,
27 m, CH_2S), 2.16 (2H, m, $2 \times CHCO$), 1.38 (2H, m), 0.91 (1H,
28 m, $CH_2CH(CH_3)_2$), 0.81 (3H, d, $J = 6\text{Hz}$, $CH(CH_3)_2$), and
29 0.74 (3H, d, $J = 6\text{Hz}$, $CH(CH_3)_2$).
30
31
32
33

1 Example 19

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-acetyl)-
4 aminophenylthiomethyl)succinyl]-L-phenylalanine-N-
5 methylamide.

6

7

8

9

10

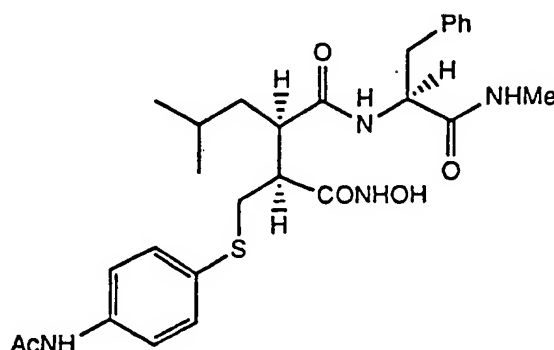
11

12

13

14

15



16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

A) [2R-isobutyl-3S-(4-aminophenylthiomethyl)succinyl]-
L-phenylalanine -N-methylamide.

Prepared by the method described in example 1f to give
material with the following characteristics.

δ_{H} (250MHz, D_6 -DMSO) 8.27 (1H, d, $J = 8.5\text{Hz}$, CONH),
7.81 (1H, m, CONHMe), 7.30 - 7.00 (5H, m, phenyl H),
6.86 (2H, d, $J = 8.5\text{Hz}$, aromatic H), 6.45 (2H, d, $J = 8.5\text{Hz}$, aromatic H), 5.25 (1H, bs, CO_2H), 4.48 (1H, m, CHCH_2Ph), 2.91 (1H, dd, $J = 14, 4\text{Hz}$, CHCH_2Ph), 2.88 (1H, dd, $J = 14, 10\text{Hz}$, CHCH_2Ph) 2.56 (3H, d, $J = 5\text{Hz}$, NHCH_3), 2.43 - 2.24 (3H, m, CH_2S and CHCO), 2.03 (1H, d, $J = 10\text{Hz}$, CHCO), 1.41 (1H, t, $J = 11\text{Hz}$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 1.26 (1H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.85 (1H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.81 (3H, d, $J = 6\text{Hz}$, $\text{CH}(\text{CH}_3)_2$), and 0.74 (3H, d, $J = 6\text{Hz}$, $\text{CH}(\text{CH}_3)_2$).

1 B) [2R-isobutyl-3S-(4-(N-acetyl)aminophenyl-thio-
2 methyl)-succinyl]-L-phenylalanine-N-methylamide.

3
4 The product from above (350mg, 0.74 mmol) was dissolved
5 in DCM (5 ml) cooled in an ice bath then triethylamine
6 (75mg, 0.74 mmol), DMAP (91mg, 7.4 mmol) and finally
7 acetic anhydride (83mg, 8.2 mmol) were added and the
8 solution stirred at RT for 90 minutes. The mixture was
9 partitioned between ethyl acetate and citric acid then
10 the organic layer washed with water and finally dried
11 over magnesium sulphate. Solvent removal gave the crude
12 product as pale yellow crystals (160mg, 0.31 mmol,
13 42%).

14
15 δ_{H} (250MHz, D_6 -DMSO) 9.94 (1H, s, CO_2H), 8.34 (1H,
16 d, $J = 8.5\text{Hz}$, CONH), 7.90 (1H, m, CONHMe), 7.46 (2H, d,
17 $J = 8.5\text{Hz}$, aromatic H) 7.30 - 7.00 (5H, m, phenyl H),
18 6.96 (2H, d, $J = 8.5\text{Hz}$, aromatic H), 4.57 (1H, m,
19 CHCH_2Ph), 2.91 (1H, dd, $J = 14, 4\text{Hz}$, CHCH_2Ph), 2.88 (1H,
20 bt, $J = 13\text{Hz}$, CHCH_2Ph), 2.58 (3H, d, $J = 5\text{Hz}$, NHCH_3),
21 2.43 - 2.16 (3H, m, CH_2S and CHCO), 2.10 (1H, d, $J =$
22 14Hz , CHCO), 1.35 (1H, t, $J = 14\text{Hz}$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 1.26
23 (1H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.86 (1H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.81
24 (3H, d, $J = 6\text{Hz}$, $\text{CH}(\text{CH}_3)_2$), and 0.74 (3H, d, $J =$
25 6Hz , $\text{CH}(\text{CH}_3)_2$).

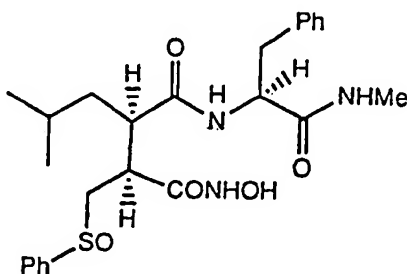
26
27 C) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-acetyl)-
28 aminophenylthiomethyl)succinyl]-L-phenylalanine-N-
29 methylamide.

30
31 Prepared by the method described in example 1g to give
32 material with the following characteristics.
33

1 m.p. 201 -202°C (dec.)
 2
 3 $[\alpha]_D = -7.5^\circ$ (c=1.0, methanol)
 4
 5 δ_H (250MHz, D_6 -DMSO) 9.90 (1H, s, $NH\bar{O}H$), 8.82 (1H,
 6 s, $NH\bar{O}H$), 8.30 (1H, d, $J = 8.5Hz$, $CONH$), 7.85 (1H, m,
 7 $CONHMe$), 7.45 (2H, d, $J = 8.5Hz$, aromatic H), 7.28 -
 8 6.94 (5H, m, phenyl H), 6.90 (2H, d, $J = 8.5Hz$,
 9 aromatic H), 4.66 (1H, m, $CHCH_2Ph$), 2.90 (1H, dd, $J =$
 10 14,4Hz, $CHCH_2Ph$), 2.76 (1H, bt, $J = 13Hz$, $CHCH_2Ph$),
 11 2.50 (3H, d, $J = 5Hz$, $NHCH_3$), 2.49 - 2.35 (2H, m,
 12 CH_2S), 2.14 (1H, m, $CHCO$), 2.03 (4H, s + m, $COCH_3$ and
 13 $CHCO$), 1.35 (2H, m), 0.86 (1H, m, $CH_2CH(CH_3)_2$), 0.81
 14 (3H, d, $J = 6Hz$, $CH(CH_3)_2$), and 0.74 (3H, d, $J = 6Hz$,
 15 $CH(CH_3)_2$).

16
 17 Example 20

18
 19 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulfinyl-
 20 methylsuccinyl]-L-phenylalanine-N-methylamide.



31 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylthiomethyl-
 32 succinyl]-L-phenylalanine-N-methylamide (250mg,
 33 0.53mmol) was dissolved in methanol (50 ml) and meta-

1 chloroperbenzoic acid (100mg, 0.58 mmol) was added.
2 After stirring for 1h at room temperature ether was
3 added and the mixture filtered. Solvent removal gave
4 the crude white solid which was recrystallised from
5 methanol / water then slurried in ether to remove final
6 traces of meta-chlorobenzoic acid to give the desired
7 material (70 mg, 0.014 mmol, 27%).

8

9 m.p. 186 -188°C

10

11 $[\alpha]_D = -13.6^\circ$ (c=0.5, methanol)

12

13 Analysis calculated for $C_{25}H_{33}N_3O_5S \cdot 0.5H_2O$

14 Requires: C60.46 H6.90 N8.46

15 Found: C60.58 H6.69 N8.29

16

17 $\delta_{H\text{H}}$ (250MHz, D_6 -DMSO, mixture of diastereomers) 9.04
18 + 8.93 (1H, 2xs, $NH\text{OH}$), 8.29 + 8.16 (1H, 2xd, $J = 8.5$
19 Hz, $CONH$), 7.79 (1H, m, $CONHMe$), 7.90 - 7.40 (8H, m,
20 aromatic H), 7.06 + 6.82 (2H, 2xm, SO-Aromatic), 4.37
21 (1H, m, $CHCH_2Ph$), 2.93 - 2.58 (3H, m, containing
22 $CHCH_2Ph$), 2.52 (3H, m, $NHCH_3$), 2.49 + 2.37 (1H, 2xm),
23 1.49 - 1.25 (2H, m, $CH_2CH(CH_3)_2$ and $CH_2CH(CH_3)_2$), 0.95
24 (1H, m, $CH_2CH(CH_3)_2$), 0.81 (3H, d, $J = 6\text{Hz}$, $CH(CH_3)_2$),
25 and 0.74 (3H, d, $J=6\text{Hz}$, $CH(CH_3)_2$).

26

27 $\delta_{C\text{C}}$ (63.9MHz, D_6 -DMSO, mixture of diastereomers)
28 172.2, 171.4, 171.3, 167.7, 144.5, 138.0, 137.9, 131.3,
29 130.9, 129.6, 129.3, 129.1, 128.8, 128.3, 127.8, 126.5,
30 126.2, 124.3, 123.6, 59.8, 58.1, 54.3, 54.0, 46.2,
31 45.8, 41.6, 40.9, 37.6, 37.4, 25.6, 25.0, 24.3, 24.2,
32 21.7, and 21.6.

33

1 Example 21

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulfonyl-
4 methylsuccinyl]-L-phenylalanine-N-methylamide.

5

6

7

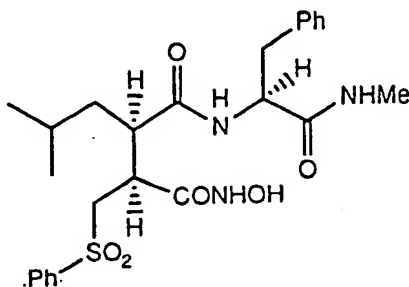
8

9

10

11

12



13 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylthiomethyl-
14 succinyl]-L-phenylalanine-N-methylamide (50mg,
15 0.11mmol) was dissolved in methanol (12 ml) and meta-
16 chloroperbenzoic acid (40mg, 0.23 mmol) was added.
17 After stirring for 3h at room temperature ether was
18 added and the mixture filtered. Solvent removal gave
19 the crude white solid which was slurried in ether to
20 remove final traces of meta-chlorobenzoic acid to give
21 the desired material.

22

23 m.p. 228 - 231°C

24

25 $[\alpha]_D = 16.8^\circ$ (c=0.5, methanol)

26

27 Analysis calculated for $C_{25}H_{33}N_3O_6S \cdot 0.3H_2O$

28 Requires: C58.99 H6.65 N8.25

29 Found: C58.92 H6.51 N8.05

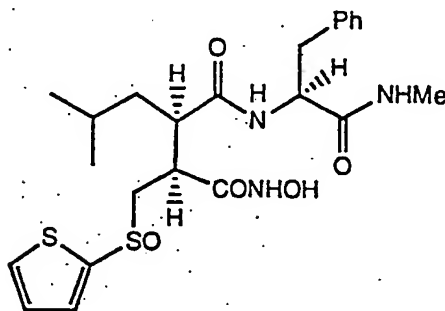
30

31 δ_{H} (250MHz, D_6 -DMSO) 8.66 (1H, s, NHOH), 8.25 (1H,
32 d, $J = 8.5$ Hz, CONH), 7.83 (1H, m, CONHMe), 7.75 - 7.50
33 (5H, m, aromatic H), 7.30 7.05 (5H, m, aromatic H),

1 4.36 (1H, m, CHCH_2Ph), 2.86 (1H, dd, $J = 14, 5$ Hz,
2 CHCH_2Ph), 2.75 (1H, dd, $J = 14, 10$ Hz, CHCH_2Ph), 2.54
3 (3H, d, $J = 4.5$ Hz, NHCH_3), 2.54 (2H, m), 1.30 (2H, m,
4 $\text{CH}_2\text{CH}(\text{CH}_3)_2$ and $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.86 (1H, m,
5 $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.75 (3H, d, $J = 6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.71
6 (3H, d, $J = 6$ Hz, $\text{CH}(\text{CH}_3)_2$).
7

8 Example 22

9
10 [4-(N-Hydroxyamino)-2R-isobutyl-3S-
11 thiophenylsulphinylmethyl-succinyl]-L-phenylalanine-N-
12 methylamide



13
14
15
16
17
18
19
20
21
22 [4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenylthio-
23 methyl-succinyl]-L-phenylalanine-N-methylamide (50mg,
24 0.11mmol) was treated as described in example 21 to
25 yield the title compound (16mg, 0.03 mmol, 29%) as a
26 mixture of diastereomer with the following
27 characteristics:

28
29 m.p. 195 -197°C (dec.)

30
31 Analysis calculated for $\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_5\text{S}_2 \cdot 0.5\text{H}_2\text{O}$

32 Requires: C54.96 H6.42 N8.36

33 Found: C54.91 H6.23 N8.23

1 δ_{H} (250MHz, D_6 -DMSO, mixture of diastereomers) 9.04
2 + 8.96 (1H, 2xs, NHOH), 8.34 + 8.29 (1H, 2xd, $J = 8.5$
3 Hz, CONH), 8.02 + 7.98 (1H, 2xm, CONHMe), 7.81 (1H, bs,
4 thiophene-H), 7.42 (1H, s, thiophene-H), 7.25 - 7.15
5 (5H, m, phenyl), 7.03 (1H, bs, thiophene-H), 4.43 (1H,
6 m, CHCH_2Ph), 3.0 - 2.6 (4H, m, containing CHCH_2Ph),
7 2.52 (7H, m, containing NHCH_3), 2.05 (1H, m), 1.6 - 1.2
8 (2H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$ and $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.87 (1H, m,
9 $\text{CH}_2\text{CH}(\text{CH}_3)_2$), and 0.85 - 0.71 (6H, m, $\text{CH}(\text{CH}_3)_2$).

10

11 Example 23

12

13 [4-(N-Hydroxyamino)-2R-isobutyl-3S-
14 thiophenylsulphonylmethyl-succinyl]-L-phenylalanine-N-
15 methylamide.

16

17

18

19

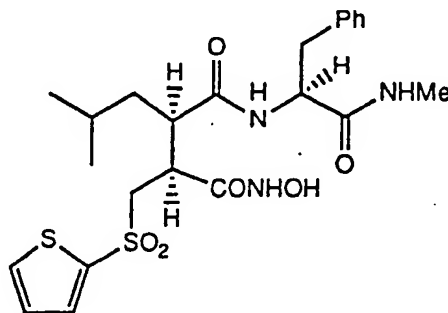
20

21

22

23

24



25 [4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenylthio-
26 methyl-succinyl]-L-phenylalanine-N-methylamide (75mg,
27 0.16mmol) was treated as described in example 22 to
28 yield the title compound (40mg, 0.08 mmol, 49%) with
29 the following characteristics:

30

31 m.p. 215 - 216°C

32

33 Analysis calculated for $\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_6\text{S}_2$

1 Requires: C54.21 H6.13 N8.24

2 Found: C54.07 H6.19 N8.04

3

4 δ_H (250MHz, D_6 -DMSO) 8.87 (1H, s, NH_{OH}), 8.25 (1H,
5 d, $J = 8.5$ Hz, $CONH$), 8.09 (1H, d, $J = 4.7$ Hz,
6 thiophene-H), 7.83 (1H, m, $CONHMe$), 7.53 (1H, d, $J = 3$
7 Hz, thiophene H), 7.25 - 7.12 (6H, m, phenyl and
8 thiophene-H), 4.36 (1H, m, $CHCH_2Ph$), 3.38 (1H, dd, $J =$
9 14,11 Hz, SCH_2), 2.87 (1H, dd, $J = 14,5$ Hz, $CHCH_2Ph$),
10 2.75 (1H, dd, $J = 14,10$ Hz, $CHCH_2Ph$), 2.70 - 2.36 (6H,
11 m, containing $NHCH_3$), 1.20 (2H, m, $CH_2CH(CH_3)_2$ and
12 $CH_2CH(CH_3)_2$), 0.89 (1H, m, $CH_2CH(CH_3)_2$), and 0.75 (6H,
13 m, $CH(CH_3)_2$).

14

15 δ_C (63.9MHz, D_6 -DMSO) 172.0, 171.2, 166.5, 140.0,
16 138.0, 135.4, 134.6, 129.0, 128.4, 128.2, 126.6, 54.3,
17 45.6, 37.5, 25.6, 25.0, 24.2, and 21.7.

18

19 Example 24

20

21 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulfonyl-
22 methylsuccinyl]-L-phenylalanine-N-methylamide sodium
23 salt.

24

25

26

27

28

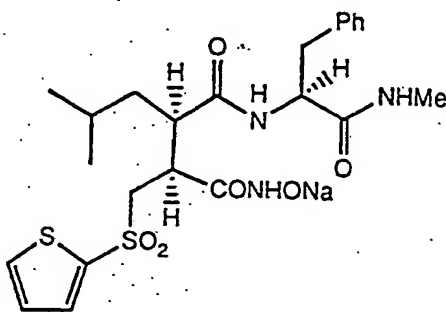
29

30

31

32

33



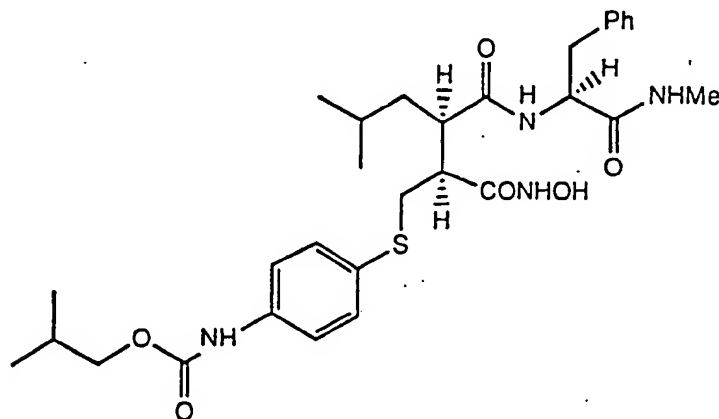
[4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulfonyl-

1 methylsuccinyl]-L-phenylalanine-N-methylamide (50mg,
 2 0.1mmol) was dissolved in methanol (10ml) and sodium
 3 hydroxide solution (0.1M, 1.0ml) added to give a
 4 homogeneous solution. The methanol was removed under
 5 reduced pressure then the residual aqueous solution
 6 freeze dried to give the title compound (40mg).

7
 8 δ_{H} (250MHz, D_6 -DMSO) 8.66 (1H, s, NH_2), 8.25 (1H,
 9 d, $J = 8.5$ Hz, CONH), 7.83 (1H, m, CONHMe), 7.75 - 7.50
 10 (5H, m, aromatic H), 7.30 7.05 (5H, m, aromatic H),
 11 4.36 (1H, m, CHCH_2Ph), 2.86 (1H, dd, $J = 14, 5$ Hz,
 12 CHCH_2Ph), 2.75 (1H, dd, $J = 14, 10$ Hz, CHCH_2Ph), 2.54
 13 (3H, d, $J = 4.5$ Hz, NHCH_3), 2.54 (2H, m), 1.30 (2H, m,
 14 $\text{CH}_2\text{CH}(\text{CH}_3)_2$ and $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.86 (1H, m,
 15 $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.75 (3H, d, $J = 6$ Hz, $\text{CH}(\text{CH}_3)_2$), and 0.71
 16 (3H, d, $J = 6$ Hz, $\text{CH}(\text{CH}_3)_2$).

17
 18 Example 25

19
 20 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(isobutyloxy-
 21 carbonylamino)phenyl)thiomethyl-succinyl]-L-phenyl-
 22 alanine-N-methylamide



33 a) [4-Hydroxy-2R-isobutyl-3S-(4-aminophenyl)thio-

1 methylsuccinyl]-L-phenylalanine-N-methylamide was
2 prepared by the method described in example 1f to give
3 a compound with the following characteristics.

4
5 δ_{H} (250MHz, D_6 -DMSO) 8.26 (1H, d, $J = 8.5$ Hz,
6 CONH), 7.81 (1H, m, CONHMe), 7.27 - 7.15 (5H, m, phenyl
7 H), 6.85 (2H, d, $J = 8.5$ Hz, aromatic H), 6.46 (2H, d, J
8 = 8.5Hz, aromatic H), 5.2 (1H, bs, CO_2H), 4.48 (1H, m,
9 CHCH_2Ph), 2.90 (1H, dd, $J = 13.5, 4.3$ Hz, CHCH_2Ph), 2.75
10 (1H, dd, $J = 13.6, 10$ Hz, CHCH_2Ph), 2.56 (3H, d, $J =$
11 4.5 Hz, NHCH_3), 2.50 - 2.25 (3H, m), 2.03 (1H, d, $J =$
12 10 Hz), 1.41 (1H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 1.26 (1H, m,
13 $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.86 (1H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.75 (3H, d, J
14 = 6Hz, $\text{CH}(\text{CH}_3)_2$), and 0.71 (3H, d, $J = 6$ Hz, $\text{CH}(\text{CH}_3)_2$).

15
16 b) N,N-Dimethylglycine (100mg, 0.97 mmol) was stirred
17 in dry THF (50ml) and triethylamine (108mg, 1.1mmol)
18 and isobutylchloroformate (146mg, 1.1mmol) were added.
19 After 1h the product from example 26a (500mg, 1.1mmol)
20 was added and the mixture stirred for a further 1h. The
21 reaction was worked up by partitioning between citric
22 acid and ethyl acetate, drying the organic layer and
23 solvent removal to give the crude product (1g).
24 Solution of the crude solid in ethyl acetate then
25 precipitation with ether resulted in white crystals of
26 the isobutylchloroformate derivative.

27
28 c) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(isobutyloxy-
29 carbonylamino) phenyl)thiomethyl-succinyl]-L-phenyl-
30 alanine-N-methylamide

31
32 The product from example 26b was converted to the
33 hydroxamic acid as described in example 1g. to give a
compound with the following characteristics.

1 m.p. 198 - 200°C

2

3 $[\alpha]_D = -8.5^\circ$ (c=1, methanol)

4

5 Analysis calculated for $C_{30}H_{42}N_4O_6S$

6 Requires: C61.41 H7.22 N9.55

7 Found: C62.04 H7.32 N9.67

8

9 δ_H (250MHz, D_6 -DMSO) 9.60 (1H, s, $NHOH$), 8.83 (1H,
10 s, $NHOH$), 8.31 (1H, d, $J = 8.5$ Hz, $CONH$), 7.85 (1H, m,
11 $CONHMe$), 7.36 - 7.25 (4H, m, aromatic H), 7.14 - 7.05
12 (3H, m, aromatic H), 6.91 (2H, d, $J = 8.5$ Hz, aromatic
13 H), 4.56 (1H, m, $CHCH_2Ph$), 3.87 (2H, d, $J = 7$ Hz,
14 $OCH_2CH(CH_3)_2$), 2.92 (1H, dd, $J = 13.7, 4.0$ Hz, $CHCH_2Ph$),
15 2.76 (1H, dd, $J = 13.6, 10$ Hz, $CHCH_2Ph$), 2.58 (3H, d, J
16 $= 4.5$ Hz, $NHCH_3$), 2.50 - 2.34 (2H, m), 2.16 - 1.87 (3H,
17 m), 1.35 (2H, m, $CH_2CH(CH_3)_2$ and $CH_2CH(CH_3)_2$), 0.93
18 (6H, d, $J = 6.6$ Hz, $OCH_2CH(CH_3)_2$), 0.87 (1H, m,
19 $CH_2CH(CH_3)_2$), 0.75 (3H, d, $J = 6$ Hz, $CH(CH_3)_2$), and
20 0.71 (3H, d, $J = 6$ Hz, $CH(CH_3)_2$).

21

22

23 Example 26

24

25 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-methyl-N-
26 (tert-butoxycarbonyl)-glycylamino) phenyl)thiomethyl-
27 succinyl]-L-phenylalanine-N-methylamide.

28

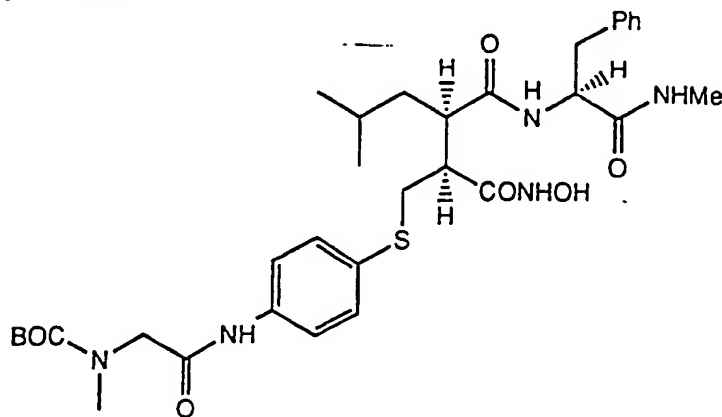
29

30

31

32

33



1 a) [4-Hydroxy-2R-isobutyl-3S-(4-(N-methyl-N-(tert-
2 butoxycarbonyl)glycylamino) phenyl)thiomethyl-
3 succinyl]-L-phenylalanine-N-methylamide was prepared as
4 described in example 26b by substitution of N-BOC
5 sarcosine for the acid component.

6
7 δ_{H} (250MHz, D_6 -DMSO) 9.97 (1H, s, CO_2H), 8.36 (1H,
8 d, $J = 8.5$ Hz, CONH), 7.91 (1H, m, CONHMe), 7.48 (2H,
9 d, $J = 8.5$ Hz, aromatic H), 7.40 - 7.05 (5H, m, aromatic
10 H), 6.97 (2H, d, $J = 8.5$ Hz, aromatic H), 4.58 (1H, m,
11 CHCH_2Ph), 3.95 (2H, d, $J = 9$ Hz, NCH_2CO), 2.92 (4H, m+d,
12 CHCH_2Ph and BOCNCH_3), 2.76 (1H, dd, $J = 13, 10$ Hz,
13 CHCH_2Ph), 2.58 (3H, d, $J = 4.5$ Hz, NHCH_3), 2.50 - 2.09
14 (4H, m), 1.46 - 1.33 (11H, m + 2xs, $(\text{CH}_3)_3\text{C}$,
15 $\text{CH}_2\text{CH}(\text{CH}_3)_2$ and $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.87 (1H, m,
16 $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.75 (3H, d, $J = 6$ Hz, $\text{CH}(\text{CH}_3)_2$), and
17 0.71 (3H, d, $J = 6$ Hz, $\text{CH}(\text{CH}_3)_2$).

18
19 b) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-methyl- N-
20 (tert-butoxycarbonyl)-glycylamino)phenyl)- thiomethyl-
21 succinyl]-L-phenylalanine-N-methylamide was prepared
22 from the material produced in example 27a as described
23 in example 1g.

24
25 δ_{H} (250MHz, D_6 -DMSO) 9.97 (1H, s, CONHOH), 8.83
26 (1H, s, NHOH), 8.32 (1H, d, $J = 8.5$ Hz, CONH), 7.86
27 (1H, m, CONHMe), 7.46 (2H, d, $J = 8.5$ Hz, aromatic H),
28 7.28 - 7.00 (5H, m, aromatic H), 6.97 (2H, d, $J =$
29 8.5Hz, aromatic H), 4.56 (1H, m, CHCH_2Ph), 3.94 (2H, d,
30 $J = 9$ Hz, NCH_2CO), 2.87 (4H, m+d, CHCH_2Ph and BOCNCH_3),
31 2.76 (1H, m, CHCH_2Ph), 2.57 (3H, d, $J = 4.5$ Hz, NHCH_3),
32 2.25 - 1.91 (2H, m), 1.42 - 1.30 (11H, m + 2xs,
33 $(\text{CH}_3)_3\text{C}$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$ and $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.92 (1H, m,
 $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.80 (3H, d, $J = 6$ Hz, $\text{CH}(\text{CH}_3)_2$), and
0.73 (3H, d, $J = 6$ Hz, $\text{CH}(\text{CH}_3)_2$).

1
2 Example 27

3
4 Collagenase inhibition activity

5
6 The potency of compounds of general formula I to act
7 as inhibitors of collagenase (a metalloproteas
8 involved in tissue degradation) was determined by the
9 procedure of Cawston and Barrett, (Anal. Biochem., 99,
10 340-345, 1979), hereby incorporated by reference,
11 whereby a 1mM solution of the inhibitor being tested or
12 dilutions thereof was incubated at 37° for 16 hours
13 with collagen and collagenase (buffered with 25mM
14 Hepes, pH 7.5 containing 5mM CaCl₂, 0.05% Brij 35 and
15 0.02% NaN₃). The collagen was acetylated ¹⁴C collagen
16 prepared by the method of Cawston and Murphy (Methods
17 in Enzymology, 80, 711, 1981), hereby incorporated by
18 reference. The samples were centrifuged to sediment
19 undigested collagen and an aliquot of the radioactive
20 supernatant removed for assay on a scintillation
21 counter as a measure of hydrolysis. The collagenase
22 activity in the presence of 1 mM inhibitor, or a
23 dilution thereof, was compared to activity in a control
24 devoid of inhibitor and the results reported below as
25 that inhibitor concentration effecting 50% inhibition
26 of the collagenase (IC₅₀).

27

<u>Compound of Example No.</u>	<u>IC₅₀</u>
1	20 nM
2	8 nM
5	3 nM
6	(50% @ 1 mM)

32
33

1
2 Example 28

3
4 Stromelysin inhibition activity

5
6 The potency of compounds of general formula I to act as
7 inhibitors of stromelysin was determined using the
8 procedure of Cawston et al (Biochem. J., 195, 159-165
9 1981), hereby incorporated by reference, whereby a 1mM
10 solution of the inhibitor being tested or dilutions
11 thereof was incubated at 37°C for 16 hours with
12 stromelysin and ¹⁴C acetylate casein (buffered with
13 25mM Hepes, pH 7.5 containing 5mM CaCl₂, 0.05% Brij 35
14 and 0.02% NaN₃. The casein was ¹⁴C acetylated
15 according to the method described in Cawston et al
16 (Biochem. J., 195, 159-165, 1981), hereby incorporated
17 by reference. The stromelysin activity in the presence
18 of 1mM, or a dilution thereof, was composed to activity
19 in a control devoid of inhibitor and the results
20 reported below as that inhibitor concentration
21 effecting 50% inhibition of the stromelysin (IC₅₀).
22

<u>Compound of Example No.</u>	<u>IC₅₀</u>
1	10 nM
2	20 nM

26
27 Examples of unit dosage compositions are as follows:
28
29
30
31
32
33

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33

Example 29

Capsules:

		Per 10,000
<u>Ingredients</u>	<u>Per Capsule</u>	<u>Capsules</u>
1. Active ingredient		
Cpd. of Form. I	40.0 mg	400 g
2. Lactose	150.0 mg	1500 g
3. Magnesium		
stearate	<u>4.0 mg</u>	<u>40 g</u>
	194.0 mg	1940 g

Procedure for capsules:

- Step 1. Blend ingredients No. 1 and No. 2 in a suitable blender.
- Step 2. Pass blend from Step 1 through a No. 30 mesh (0.59 mm) screen.
- Step 3. Place screened blend from Step 2 in a suitable blender with ingredient No. 3 and blend until the mixture is lubricated.
- Step 4. Fill into No. 1 hard gelatin capsule shells on a capsule machine.

1 Example 30

2

3

Tablets:

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

Per 10,000

IngredientsPer TabletTablets

1. Active ingredient

Cpd. of Form. I 40.0 mg

400 g

2. Corn Starch 20.0 mg

200 g

3. Alginic acid 20.0 mg

200 g

4. Sodium alginate 20.0 mg

200 g

5. Magnesium

stearate 1.3 mg13 g

101.3 mg

1013 g

Procedure for tablets:

Step 1. Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2. Add sufficient water portionwise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3. The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38) screen.

Step 4. The wet granules are then dried in an oven at 140°F (60°C) until dry.

Step 5. The dry granules are lubricated with ingredient No. 5.

Step 6. The lubricated granules are compressed on a suitable tablet press.

1 Example 31

2

3 Intramuscular Injection:

4	<u>Ingredient</u>	<u>Per ml.</u>	<u>Per liter</u>
5	1. Compound of Formula I		
6	Active ingredient	10.0 mg	10 g
7	2. Istonic buffer		
8	solution pH 4.0.	q.s.	q.s.

9

10 Procedure:

11 Step 1. Dissolve the active ingredient in the buffer
12 solution.

13 Step 2. Aseptically filter the solution from Step 1.

14 Step 3. The sterile solution is now aseptically
15 filled into sterile ampoules.

16 Step 4. The ampoules are sealed under asptic
17 conditions.

18

19 Example 32

20

21 Suppositories:

22		Per
23	<u>Ingredients</u>	<u>1,000 Supp</u>
24	1. Compound of Form. I	
25	Active ingredient	40 g
26	2. Polyethylene Glycol	
27	1000	1,350 g
28	3. Polyethylene Glycol	
29	4000	<u>450 g</u>
30		1,840 g

31

32

33

1 Procedure:

2 Step 1. Melt ingredient No. 2 and No. 3 together and
3 stir until uniform.

4 Step 2. Dissolve ingredient No. 1 in the molten mass
5 from Step 1 and stir until uniform.

6 Step 3. Pour the molten mass from Step 2 into
7 suppository moulds and chill.

8 Step 4. Remove the suppositories from moulds and
9 wrap.

10

11 Example 33

12

13 Eye Ointment

14

15 An appropriate amount of a compound of general formula
16 I is formulated into an eye ointment base having the
17 following composition:

18

19	Liquid paraffin	10%
20	Wool fat	10%
21	Yellow soft paraffin	80%

22

23 Example 34

24

25 Topical skin ointment.

26

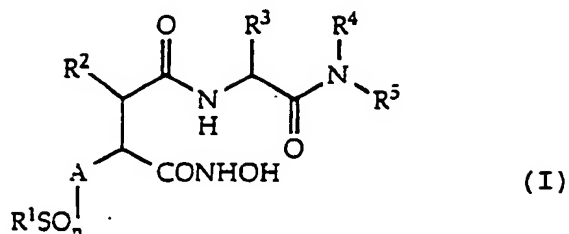
27 An appropriate amount of a compound of general formula
28 I is formulated into a topical skin ointment base
29 having the following composition:

30

31	Emulsifying wax	30%
32	White soft paraffin	50%
33	Liquid paraffin	20%

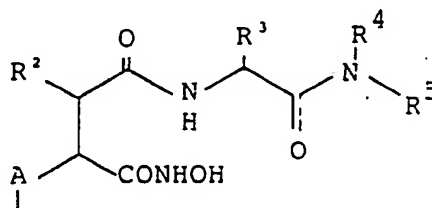
1 CLAIMS

2
3 1. A compound of general formula I:



11 wherein:

12
13 R^1 represents a C_1 - C_6 alkyl, phenyl, thiophenyl,
14 substituted phenyl, phenyl(C_1 - C_6)alkyl,
15 heterocyclyl, (C_1 - C_6)alkylcarbonyl or phenacyl or
16 substituted phenacyl group; or when $n = 0$, R^1
17 represents SR^x , wherein R^x represents a group:



26 R^2 represents a hydrogen atom or a C_1 - C_6 alkyl, C_1 - C_6
27 alkenyl, phenyl(C_1 - C_6)alkyl,
28 cycloalkyl(C_1 - C_6)alkyl or cycloalkenyl(C_1 - C_6)alkyl
29 group;

30
31 R^3 represents an amino acid side chain or a C_1 - C_6
32 alkyl, benzyl, (C_1 - C_6 alkoxy)benzyl or
33 benzyloxy(C_1 - C_6 alkyl) or benzyloxy benzyl group;

- 1 R^4 represents a hydrogen atom or a C_1-C_6 alkyl group;
2
3 R^5 represents a hydrogen atom or a methyl group;
4
5 n is an integer having the value 0, 1 or 2; and
6
7 A represents a C_1-C_6 hydrocarbon chain, optionally
8 substituted with one or more C_1-C_6 alkyl, phenyl
9 or substituted phenyl groups;
10
11 or a salt thereof.
12
13 2. A compound as claimed in Claim 1, in which the
14 chiral centre adjacent the substituent R^3 has S
15 stereochemistry.
16
17 3. A compound as claimed in Claim 1 or 2, wherein the
18 chiral centre adjacent the substituent R^2 has R
19 stereochemistry.
20
21 4. A compound as claimed in Claim 1, 2 or 3, in which
22 R^1 represents a hydrogen atom or a C_1-C_4 alkyl, phenyl,
23 thiophenyl, benzyl, acetyl or phenacyl group.
24
25 5. A compound as claimed in any one of Claims 1 to 4,
26 wherein R^2 represents a C_3-C_6 alkyl group.
27
28 6. A compound as claimed in any one of Claims 1 to 5,
29 wherein R^3 represents a benzyl or
30 4-(C_1-C_6)alkoxyphenylmethyl or benzyloxybenzyl group.
31
32 7. A compound as claimed in any one of Claims 1 to 6,
33 wherein R^4 represents a C_1-C_4 alkyl group.

1 8. A compound as claimed in any one of Claims 1 to 7,
2 wherein R⁵ represents a hydrogen atom.

3
4 9. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthio-
5 methyl)-succinyl]-L-phenylalanine-N-methylamide,

6
7 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthio-
8 methyl) succinyl]-L-phenylalanine-N-methylamide,

9
10 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(benzylthiomethyl)
11 succinyl]-L-phenylalanine-N-methylamide,

12
13 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(acetylthiomethyl)
14 succinyl]-L-phenylalanine-N-methylamide or

15
16 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiolmethyl)
17 succinyl]-L-phenylalanine-N-methylamide

18
19 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(pivaloylthiomethyl)
20 succinyl]-L-phenylalanine-N-methylamide

21
22 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)
23 succinyl]-L-phenylalanine-N-methylamide sodium salt

24
25 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenyl-
26 thiomethyl)succinyl]-L-phenylalanine-N-methylamide

27
28 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenyl-
29 thiomethyl)succinyl]-L-phenylalanine-N-methylamide

30
31 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thiophenethio-
32 methyl)succinyl]-L-phenylalanine-N-methylamide sodium
33 salt

- 1 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenyl-
- 2 thiomethyl) succinyl]-L-phenylalanine-N-methylamide
- 3 sodium salt
- 4
- 5 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-tertbutylphenyl-
- 6 thiomethyl) succinyl]-L-phenylalanine-N-methylamide
- 7
- 8 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2,4-dimethylphenyl-
- 9 thiomethyl) succinyl]-L-phenylalanine-N-methylamide
- 10
- 11 bis-S,S'-([4(N-Hydroxyamino-2R-isobutyl-3S-(thiomethyl)
- 12 succinyl]-L-phenylalanine-N-methylamide) disulphide
- 13
- 14 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-bromophenylthio-
- 15 methyl) succinyl]-L-phenylalanine-N-methylamide
- 16
- 17 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-chlorophenylthio-
- 18 methyl) succinyl]-L-phenylalanine-N-methylamide
- 19
- 20 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-methylphenylthio-
- 21 methyl) succinyl]-L-phenylalanine-N-methylamide
- 22
- 23 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-acetyl)-amino-
- 24 phenylthiomethyl) succinyl]-L-phenylalanine-N-methyl-
- 25 amide
- 26
- 27 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulphinyl-
- 28 methylsuccinyl]-L-phenylalanine-N-methylamide
- 29
- 30 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulphonyl-
- 31 methylsuccinyl]-L-phenylalanine-N-methylamide
- 32
- 33

1 [4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenylsulphinyl-
2 methyl-succinyl]-L-phenylalanine-N-methylamide

3

4 [4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenylsulphonyl-
5 methyl-succinyl]-L-phenylalanine-N-methylamide

6

7 [4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulphonyl-
8 methyl-succinyl]-L-phenylalanine-N-methylamide sodium
9 salt

10

11 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(isobutyloxy-
12 carbonylamino)phenyl)thiomethyl-succinyl]-L-phenyl-
13 alanine-N-methylamide

14

15 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-methyl-N-
16 (tert-butoxycarbonyl)-glycylamino)phenyl)thiomethyl-
17 succinyl]-L-phenylalanine-N-methylamide

18

19 or, where appropriate, a salt of such a compound.

20

21 10. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenyl-
22 thiomethyl) succinyl]-L-phenylalanine-N-methylamide, or

23

24 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiolmethyl)
25 succinyl]-L-phenylalanine-N-methylamide

26

27 or a salt thereof.

28

29 11. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenyl-
30 thiomethyl)succinyl]-L-phenylalanine-N-methylamide or a
31 salt thereof.

32

33

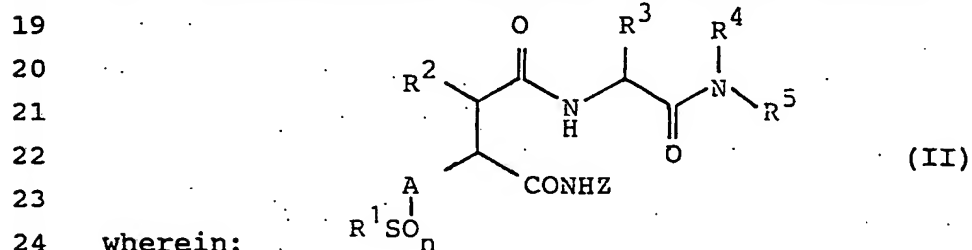
1 12. A compound as claimed in any one of claims 1 to 11
2 for use in human or veterinary medicine.

3
4 13. The use of a compound as claimed in any one of
5 claims 1 to 11 in the preparation of an agent for use
6 in the management of disease involving tissue
7 degradation and/or in the promotion of wound healing.

8
9 14. A pharmaceutical or veterinary formulation
10 comprising a compound as claimed in any one of claims 1
11 to 11 and a pharmaceutically and/or veterinarily
12 acceptable carrier.

13
14 15. A process for preparing a compound of general
15 formula I as defined in claim 1, the process
16 comprising:

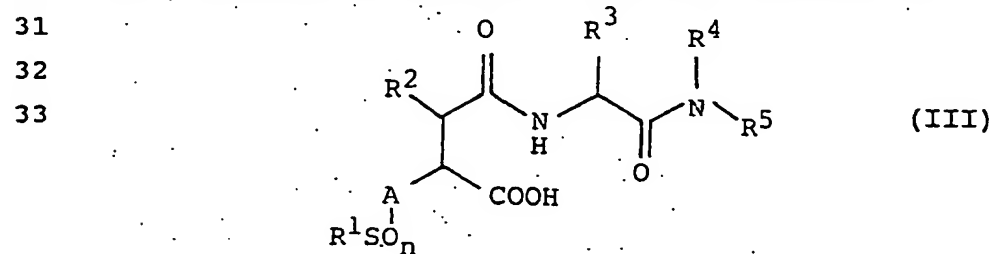
17
18 (a) deprotecting a compound of general formula II



26 wherein:

27 R^1 , R^2 , R^3 , R^4 , R^5 , A and n are as defined in
28 general formula I and Bn represents a
29 benzyloxycarbonyl group; or

30 (b) reacting a compound of general formula III



1 wherein:

2

3 R^1 , R^2 , R^3 , R^4 , R^5 , A and n are as defined in
4 general formula I,

5

6 with hydroxylamine or a salt thereof; and

7

8 (c) optionally after step (a) or step (b) converting a
9 compound of general formula I into another compound of
10 general formula I.

11

12 16. A compound of general formula II

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

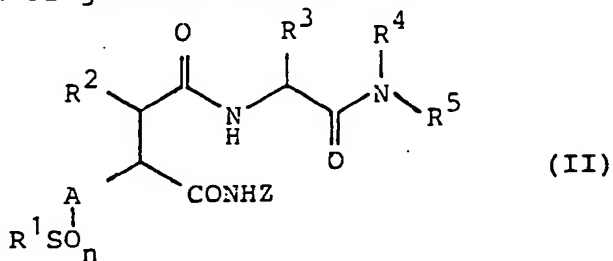
29

30

31

32

33



wherein:

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

R^1 , R^2 , R^3 , R^4 , R^5 , A and n are as defined in
general formula I and Z represents a protecting
group.

17. A compound of general formula III

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

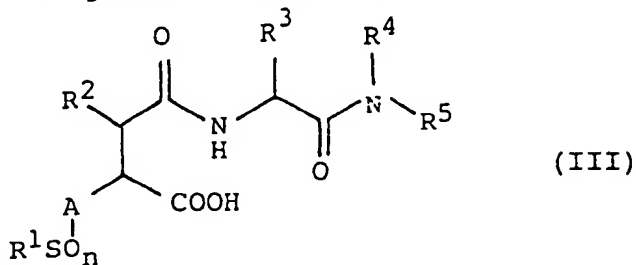
44

45

46

47

48



wherein:

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45


46

R^1 , R^2 , R^3 , R^4 , R^5 , A and n are as defined in
general formula I.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 89/01399

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC C 07 C 323/62, 323/60, C 07 D 333/34, C 07 C 327/32, IPC ⁵ : 317/50, 313/48, A 61 K 31/13, 31/38		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC ⁵	C 07 C 259/00, 323/00, C 07 D 333/00, C 07 C 327/00, 317/00, 313/00	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP, A, 0236872 (F. HOFFMANN-LA ROCHE) 16 September 1987 see claim 1 cited in the application --	1-17
A	EP, A, 0012401 (MERCK & CO. INC.) 25 June 1980 see claim 1 cited in the application --	1-17
A	DE, A, 2720996 (E.R. SQUIBB & SONS) 24 November 1977 see claim 1 cited in the application & US, A, 4105789 --	1-17
A	EP, A, 0274453 (LABORATOIRE ROGER BELLON) 13 July 1988 see claim 1 --	1-17
A	EP, A, 0214639 (G.D. SEARLE) 18 March 1987 see claim 1 ./.	1-17
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
8th March 1990	17 APR 1990	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	 MISS T. TAZELAAR	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
------------	--	----------------------

cited in the application
& US, A, 4599361

- | | | |
|---|---|------|
| A | Chemical Abstracts, volume 83, no. 7,
18 August 1975, (Columbus, Ohio, US),
J.P. Devlin et al.: "Antibiotic
actinonin. III. Synthesis of
structural analogs of actinonin by
the anhydride-imide method",
see page 549, abstract 59249e,
& J. Chem. Soc., Perkin Trans. I,
1975, (9), 830-41 | 1-17 |
|---|---|------|

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 8901399

SA 33118

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 04/04/90. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0236872	16-09-87	AU-B- 588437	14-09-89
		AU-A- 6990287	17-09-87
		JP-A- 62230757	09-10-87
EP-A- 0012401	25-06-80	AT-T- E6503	15-03-84
		AU-B- 530380	14-07-83
		AU-A- 5346179	19-06-80
		CA-C- 1262684	07-11-89
		JP-A- 55081845	20-06-80
		US-A- 4374829	22-02-83
DE-A- 2720996	24-11-77	US-A- 4105789	08-08-78
		CA-A- 1103259	16-06-81
		FR-A, B 2421874	02-11-79
		GB-A- 1575850	01-10-80
		JP-A- 52136121	14-11-77
		US-A- 4146639	27-03-79
		US-A- 4228184	14-10-80
		US-A- 4153725	08-05-79
		US-A- 4192882	11-03-80
		US-A- 4146641	27-03-79
		US-A- 4207342	10-06-80
		US-A- 4200649	29-04-80
		US-A- 4206232	03-06-80
		US-A- 4192881	11-03-80
		US-A- 4207336	10-06-80
		US-A- 4207337	10-06-80
EP-A- 0274453	13-07-88	FR-A- 2609289	08-07-88
		JP-A- 63258449	25-10-88
EP-A- 0214639	18-03-87	US-A- 4599361	08-07-86
		US-A- 4743587	10-05-88
		AU-B- 588362	14-09-89
		AU-A- 6240886	12-03-87
		JP-A- 62103052	13-05-87

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.